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(54) [(Bicyclic heterocyclyl)methyl and -hetero] substituted hexahydro-1H-azepines and pyrrolidines.

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EP-A- 0 151 824
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J. Het. Chem. (1987) 24, 31-37

J. Het. Chem. (1986) 29, 1178-1183

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Description

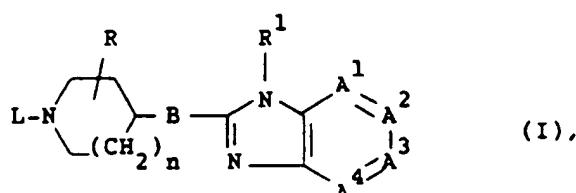
In U.S. Patent No. 4,219,559 there are described a number of 1-substituted N-heterocyclyl-4-piperidinamines as compounds having useful anti-histaminic properties.

5 In U.S. Patent Nos. 4,556,660, 4,634,704, 4,695,569 and 4,588,722 there are described further series of N-heterocyclyl-4-piperidinamines as compounds having useful anti-histaminic and serotonin-antagonistic properties.

10 In European Patent Application No. 151,826, published August 21, 1985 there are described a number of 4-(bicyclic heterocyclyl)methyl and -heteropiperidines having useful anti-histaminic and serotonin-antagonistic properties whereas in European Patent Application No. 206,415, published December 30, 1986 there are described some anti-histaminic (4-piperidinylmethyl and -hetero)purines.

The compounds of the present invention differ therefrom by the fact that they contain a pyrrolidine or hexahydro-1H-azepine moiety and by their favourable pharmacological properties.

15 The invention is concerned with novel substituted benzimidazole derivatives which can structurally be represented by the formula



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the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

-A¹ = A²-A³ = A⁴- is a bivalent radical having the formula

30 -CH = CH-CH = CH- (a-1),

-N = CH-CH = CH- (a-2),

-CH = N-CH = CH- (a-3),

-CH = CH-N = CH- (a-4),

-CH = CH-CH = N- (a-5),

35 -N = CH-N = CH- (a-6), or

-CH = N-CH = N- (a-7),

wherein one or two hydrogen atoms in said radicals (a-1) - (a-7) may, each independently from each other, be replaced by halo, C₁-₆alkyl, C₁-₆alkyloxy, trifluoromethyl or hydroxy;

40 R¹ is hydrogen, C₁-₁₀alkyl, C₃-₆cycloalkyl, Ar¹ or C₁-₆alkyl substituted with one or two Ar¹ radicals;

B is NR², CH₂, O, S, SO or SO₂; said R² being hydrogen, C₁-₆alkyl, C₃-₆cycloalkyl, C₁-₆alkylcarbonyl, C₁-₆alkyloxycarbonyl and Ar²-C₁-₆alkyl;

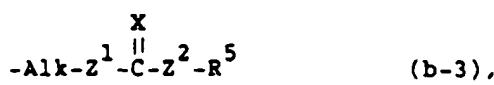
R is hydrogen or C₁-₆alkyl;

n is 0 or 2;

45 L is hydrogen, C₁-₆alkylcarbonyl, C₁-₆alkylsulfonyl, C₁-₆alkyloxycarbonyl, Ar²-C₁-₆alkyloxycarbonyl, Ar²-carbonyl, Ar²-sulfonyl, C₃-₆cycloalkyl, C₂-₆alkenyl optionally substituted with Ar², C₁-₁₂alkyl, a radical of formula

-Alk-R³ (b-1)

50 -Alk-Y-R⁴ (b-2)



or

-CH₂-CHOH-CH₂-O-R⁶ (b-4); wherein

R³ is Ar², Het, cyano, isocyanato, isothiocyanato, Ar²-sulfonyl or halo;
R⁴ is hydrogen, Ar², Het or C₁₋₆alkyl optionally substituted with halo, Ar² or Het;
R⁵ is hydrogen, Ar², Het or C₁₋₆alkyl optionally substituted with halo, Ar² or Het;
5 R⁶ is Ar² or naphthalenyl;
Y is O, S, NR⁷;
said R⁷ being hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl or Ar¹-carbonyl;
Z¹ and Z² each independently are O, S, NR⁸ or a direct bond;
said R⁸ being hydrogen or C₁₋₆alkyl;
10 X is O, S or NR⁹;
said R⁹ is hydrogen, C₁₋₆alkyl or cyano;
each Alk independently being C₁₋₆alkanediyl;
Het is a five- or six-membered heterocyclic ring containing 1, 2, 3, or 4 heteroatoms, said heteroatoms
being selected from the group consisting of oxygen, sulfur and nitrogen, provided that no more than two
15 oxygens or sulfurs are present, said five or six-membered ring being optionally condensed with a five- or
six-membered carbocyclic or heterocyclic ring also containing 1, 2, 3 or 4 heteroatoms, the latter
heteroatoms being selected from the group consisting of oxygen, sulfur and nitrogen, provided that no more
than 2 oxygens or sulfurs are present, and when said Het is a bicyclic ring system it may optionally be
20 substituted with up to 6 substituents, and when said Het is a monocyclic ring system it may optionally be
substituted with up to 3 substituents, said substituents of Het being selected from the group consisting of a
bivalent radical of formula =X; halo; isocyanato; isothiocyanato; nitro; cyano; trifluoromethyl; a radical of
formula -A; a radical of formula -Y-A; or a radical of formula -Z¹-C(=X)-Z²-A; wherein said =X indepen-
25 dently has the same meaning of the previously defined X and A is hydrogen, Ar² or C₁₋₆alkyl being
optionally substituted with Ar², C₁₋₆alkyloxy, Ar²-O, hydroxy, or C₁₋₆alkyloxycarbonyl; and Y, Z¹ and Z²
independently have the same meaning of the previously defined Y, Z¹ and Z²; provided that when in the
radical -Z¹-C(=X)-Z²-A, A is hydrogen and Z¹ is NR⁸, O or S, then Z² is other than O or S; preferably the
sum of heteroatoms in the above defined Het is less than 6;

Ar¹ is a member selected from the group consisting of phenyl, being optionally substituted with 1, 2 or
3 substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano,
30 trifluoromethyl, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, mercapto, amino, mono- and di(C₁₋₆alkyl)amino,
carboxyl, C₁₋₆alkyloxycarbonyl and C₁₋₆alkylcarbonyl; thiienyl; halothienyl; furanyl; C₁₋₆alkyl substituted
furanyl; pyridinyl; pyrimidinyl; pyrazinyl; thiazolyl and imidazolyl optionally substituted with C₁₋₆alkyl; and

Ar² is a member selected from the group consisting of phenyl being optionally substituted with 1, 2 or 3
substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano,
35 trifluoromethyl, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, mercapto, amino, mono- and di(C₁₋₆alkyl)amino,
carboxyl, C₁₋₆alkyloxycarbonyl and C₁₋₆alkylcarbonyl.

As used in the foregoing definitions the term halo is generic to fluoro, chloro, bromo and iodo; the term
"C₁₋₆alkyl" is meant to include straight and branch chained saturated hydrocarbon radicals having from 1
40 to 6 carbon atoms such as, for example, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 2-
methylpropyl, butyl, pentyl and hexyl; "C₁₋₁₂alkyl" is meant to include C₁₋₆alkyl radicals, as defined
hereinabove, and the higher homologs thereof having from 7 to 12 carbon atoms; the term "C₃₋₆cycloalkyl"
is generic to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; the term "C₂₋₆alkenyl" defines straight
45 and branch chained hydrocarbon radicals containing one double bond and having from 2 to 6 carbon atoms
such as, for example, ethenyl, 2-propenyl, 3-but enyl, 2-but enyl, 2-pentenyl, 3-pentenyl, and 3-methyl-2-
but enyl; and when a C₃₋₆alkenyl is substituted on a heteroatom, then the carbon atom of said C₃₋₆alkenyl
connected to said heteroatom preferably is saturated.

It is to be understood that the compounds of formula (I) may exist in hydrated or in solvent addition
forms and that the invention includes all such forms.

It is evident that in the compounds of formula (I) wherein R³, R⁴ or R⁵ is Het, said Het may be
50 unsaturated or partly or completely saturated.

The compounds of formula (I) wherein Het is a heterocycle which is substituted with a hydroxy, mercapto or amino radical may contain in their structure a keto-enol tautomeric system or a vinyllog system
thereof, and consequently these compounds may be present in their keto form as well as their enol form.
In particularly Het is (i) an optionally substituted five- or six-membered heterocyclic ring containing 1, 2, 3
55 or 4 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, provided that no more
than two oxygens or sulfurs are present; or Het is (ii) an optionally substituted five- or six-membered
heterocyclic ring containing 1 or 2 heteroatoms selected from the group consisting of oxygen, sulfur and
nitrogen, being ortho-condensed with an optionally substituted five- or six-membered ring through two ring

carbon atoms or one ring carbon and one ring nitrogen atom, containing in the remainder of the condensed ring only carbon atoms; or

Het is (iii) an optionally substituted five- or six-membered heterocyclic ring containing 1 or 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, being ortho-condensed with an optionally

5 substituted five- or six-membered heterocyclic ring through two ring carbon atoms or one ring carbon and one ring nitrogen atom, containing in the remainder of the condensed ring 1 or 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen; wherein Het may optionally be substituted with up to 2 substituents when Het is a monocyclic ring system, and wherein Het may optionally be substituted with up to 5 substituents when Het is a bicyclic ring system, said substituents being the same as previously

10 described.

In more detail Het is a member selected from the group consisting of pyridinyl which is optionally substituted with one or two substituents each independently selected from halo, amino, mono- and di-(C₁-₆alkyl)-amino, Ar²-C₁-₆alkylamino, nitro, cyano, aminocarbonyl C₁-₆alkyl, C₁-₆alkyloxy, C₁-₆alkylthio, C₁-₆alkyloxycarbonyl, hydroxy, C₁-₆alkylcarbonyloxy, Ar²-C₁-₆alkyl and carboxyl; pyridinyloxide optionally

15 substituted with nitro; pyrimidinyl which is optionally substituted with one or two substituents each independently selected from the group consisting of halo, amino, hydroxy, C₁-₆alkyl, C₁-₆alkyloxy, C₁-₆alkylthio and Ar²-C₁-₆alkyl; pyridazinyl which is optionally substituted with C₁-₆alkyl or halo; pyrazinyl which is optionally substituted with halo, amino or C₁-₆alkyl; thieryl which is optionally substituted with halo or C₁-₆alkyl; furanyl which is optionally substituted with halo or C₁-₆alkyl; pyrrolyl which is optionally

20 substituted with C₁-₆alkyl; thiazolyl which is optionally substituted with C₁-₆alkyl, C₁-₆alkyloxycarbonyl, Ar² or Ar²-C₁-₆alkyl; imidazolyl which is optionally substituted with one or two substituents each independently selected from C₁-₆alkyl and nitro; tetrazolyl which is optionally substituted with C₁-₆alkyl; 1,3,4-thiadiazolyl which is optionally substituted with C₁-₆alkyl; 5,6-dihydro-4H-1,3-thiazin-2-yl which is optionally substituted with C₁-₆alkyl; 4,5-dihydrothiazolyl which is optionally substituted with C₁-₆alkyl; oxazolyl which is

25 optionally substituted with C₁-₆alkyl; 4,5-dihydro-5-oxo-1H-tetrazolyl which is optionally substituted with C₁-₆alkyl; 1,4-dihydro-2,4-dioxo-3(2H)-pyrimidinyl being optionally substituted with C₁-₆alkyl; 4,5-dihydro-4-oxo-2-pyrimidinyl; 2-oxo-3-oxazolidinyl; indolyl which is optionally substituted with C₁-₆alkyl; quinolinyl which is optionally substituted with hydroxy or C₁-₆alkyl; quinazolinyl which is optionally substituted with hydroxy or C₁-₆alkyl; quinoxalinyl which is optionally substituted with C₁-₆alkyl; phthalazinyl which is

30 optionally substituted with halo; 1,3-dioxo-1H-isoindol-2(3H)-yl; 2,3-dihydro-3-oxo-4H-benzoxazinyl and 2,3-dihydro-1,4-benzodioxinyl, both being optionally substituted with C₁-₆alkyl or halo; dioxanyl being optionally substituted with C₁-₆alkyl; 2-oxo-2H-1-benzopyranyl and 4-oxo-4H-1-benzopyranyl both being optionally substituted with C₁-₆alkyl; morfolinyl; thiomorfolinyl; piperidinyl; and

a radical of formula

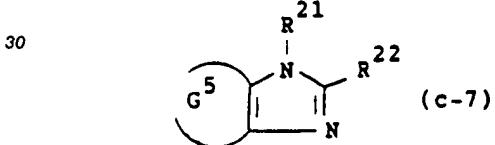
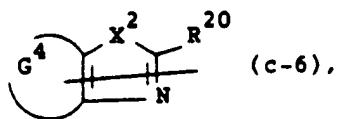
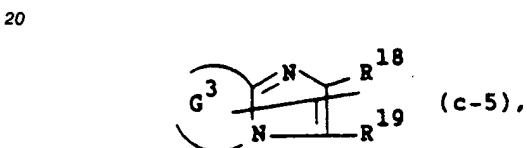
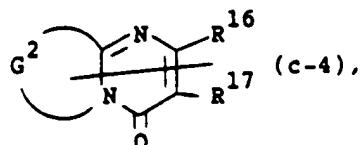
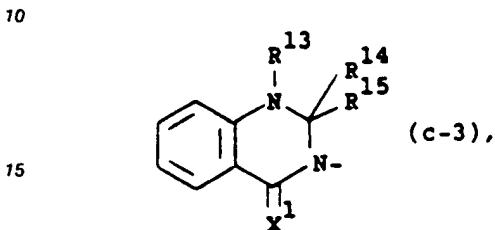
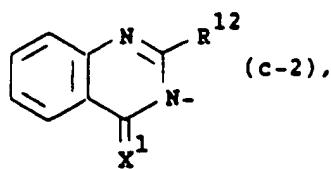
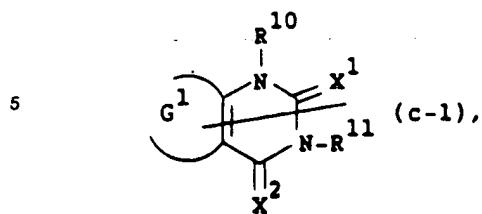
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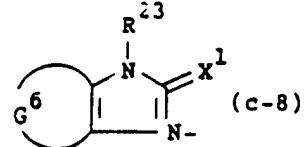
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and



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wherein X¹ and X² are each independently O or S; R¹⁰, R¹¹, R¹³, R²¹ and R²³ are each independently hydrogen, C₁₋₆alkyl, Ar²-C₁₋₆alkyl, hydroxyC₁₋₆alkyl or C₁₋₆alkoxy.

R^{12} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} and R^{22} are each independently hydrogen, C_1 - ϵ alkyl, hydroxy, mercapto, C_1 -alkyloxy, C_1 -alkylthio, halo and (C_1 -alkyloxycarbonyl)C₁-alkyl;

40 mercapto, C₁-6 alkyloxy, C₁-6 alkylthio, halo and (C₁-6 alkyloxycarbonyl)C₁-6 alkyl; G¹ is -CH = CH-CH = CH-, -S-CH = CH- or -N = CH-NH-; C² is -CH = CH-CH = CH-, S(=O)₂, S(=O)(=O) or S(=CH₂)CH = CH₂;

G² is -CH=CH-CH=CH-, -S-(CH₂)₂-, -S-(CH₂)₃-, -(CH₂)₄- or -S-CH=CH-;
G³ is -CH=CH-CH=CH-, -CH₂-NH-(CH₂)₂-, -S-CH=CH-, -S-(CH₂)₃-, -N=CH-CH=CH-, -CH=N-CH=CH-,
 -CH=CH-N=CH-, -CH=CH-CN-N=, -N=CH-N=CH- or -CH=N-CH=N-;

45 G⁴ is -CH=CH-CH=CH-, -CH=CH-CH-N=CH-, -N=CH-N=CH- or -CH=N-CH-N=CH-, -CH=CH-CH=CH-N=CH-, -CH=CH-CH-N=CH-, -N=CH-N=CH₂ or -CH=CH-N=CH-N=CH-;

$\text{CH} - \text{CH-CH} = \text{N}-$, $-\text{N} = \text{CH-N-CH} = \text{CH-CH} = \text{N}-$,
 G^5 is $-\text{CH} = \text{CH-CH} = \text{CH-}$, $-\text{N} = \text{CH-CH} = \text{CH-}$, $-\text{CH} = \text{N-CH} = \text{CH-}$, $-\text{CH} = \text{CH-N} = \text{CH-}$, $-\text{CH} = \text{CH-CH} = \text{N-}$, $-\text{N} = \text{CH-N} = \text{CH-}$ or $-\text{CH} = \text{N-CH} = \text{N-}$;

⁵⁰ G⁶ is -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-C=CH-, -CH=CH-N=CH-, -CH=CH-CH=CH=N-, -N=CH-N=CH-, -CH=N-CH=N-;

wherein one or two hydrogen atoms in said radicals G¹, G², G³, G⁴, G⁵ or G⁶ or in the benzene part of the radicals of formula (c-2) or (c-3) may be replaced by C₁₋₆alkyl, C₁₋₆alkylthio, C₁₋₆alkyloxy or halo where said hydrogen atom is bonded on a carbon atom, or by C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, Ar²-C₁₋₆alkyl, where said hydrogen is bonded on a nitrogen atom;

55 An interesting group among the compounds of formula (I) comprises those compounds of formula (I),
wherein $n = 2$.

Another interesting group among the compounds of formula (I) comprises those compounds of formula (I) wherein n = 0.

Among the above groups those compounds of formula (I) are preferred wherein Het is the particular Het described hereinabove.

More particularly preferred compounds are those particularly preferred compounds wherein R is hydrogen, R¹ is C₁₋₆alkyl substituted with one Ar¹ and B is NH or CH₂.

Especially preferred compounds are those more particularly preferred compounds wherein L is hydrogen, C₁₋₆alkyl or a radical of formula (b-1), (b-2) or (b-3) and B is NH.

More especially preferred compounds within the invention are those especially preferred compounds wherein R³, R⁴ and R⁵ are each Ar² or Het, R⁷ is hydrogen or C₁₋₆alkyl, X is O and Z¹ and Z² are each independently NH or a direct bond.

10 A particular subgroup of compounds of formula (I) comprises those compounds, preferred, particularly preferred, more particularly preferred, especially preferred and more especially preferred compounds wherein A¹ = A²-A³ = A⁴ is a bivalent radical having the formula (a-1).

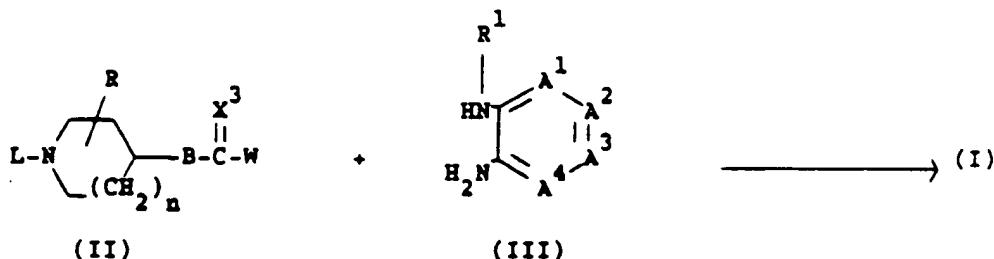
Another particular subgroup of compounds of formula (I) comprises those compounds, preferred, particularly preferred, more particularly preferred, especially preferred and more especially preferred

15 compounds wherein A¹ = A²-A³ = A⁴ is a bivalent radical having a formula (a-2) through (a-7), with (a-2) being the most interesting group.

The compounds of formula (I) can generally be prepared by reacting an intermediate of formula (II) with a diamine of formula (III).

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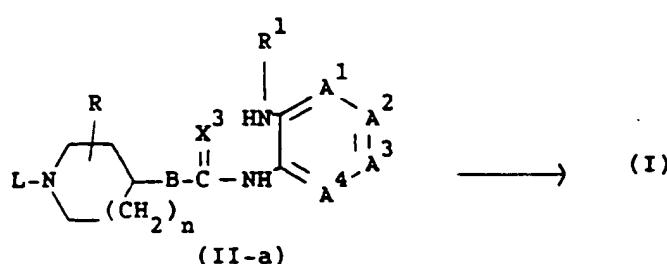


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In some instances the reaction of (II) with (III) first yields an intermediate of formula (II-a)

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which may in situ or, if desired, after isolation and purifying it, be cyclized to obtain the desired compounds of formula (I).

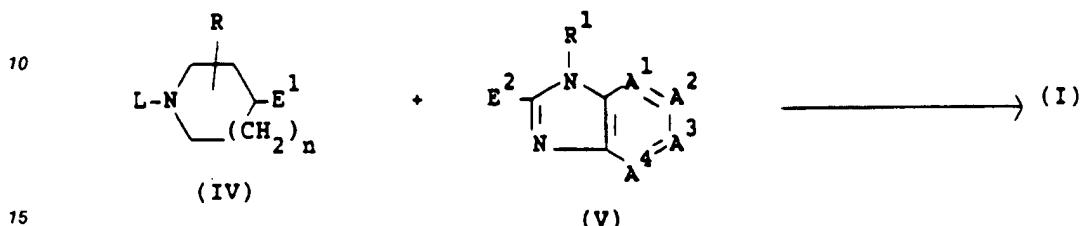
In the reaction of (II) with (III) and in the following reaction schemes W¹ and W represent an appropriate leaving group such as, for example, halo, e.g. chloro, bromo or iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy or 4-methylphenylsulfonyloxy, whereas W may also be alkoxy, alkylthio, Ar²-O- or Ar²-S-. In (II) and (II-a) X³ denotes O, S or NH.

50 The pyrrolidine or hexahydro-1H-azepine derivatives of formula (II) may in situ be generated, for example, by converting a pyrrolidine or hexahydro-1H-azepine which is substituted with a -B-C(=X³)-OH radical into an intermediate of formula (II) by reacting the former with thionyl chloride, phosphor trichloride, phosphoryl chloride, polyphosphoric acid, and phosphoroxy chloride.

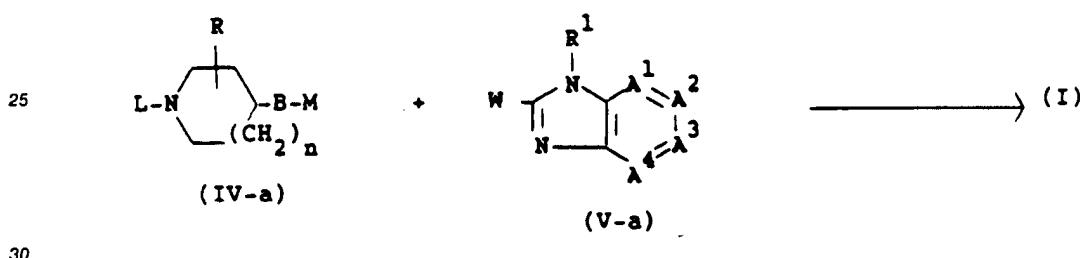
55 The reaction of (II) with (III) may be conducted in a suitable solvent such as, for example, a hydrocarbon, e.g., benzene, hexane; an ether, e.g., 1,1'-oxybisethane, tetrahydrofuran; a ketone, e.g., 2-propanone, 2-butanone; an alcohol, e.g., methanol, ethanol, 2-propanol, 1-butanol; a halogenated hydrocarbon, e.g., trichloromethane, dichloromethane, an organic acid, e.g., acetic acid, propanoic acid; a polar aprotic solvent e.g., N,N-dimethylformamide, N,N-dimethylacetamide; and mixtures of such solvents. De-

pending upon the solvent and nature of W it may be appropriate to add a suitable base and/or a iodide salt, preferably an alkali metal iodide, to the reaction mixture. Elevated temperatures may enhance the reaction rate.

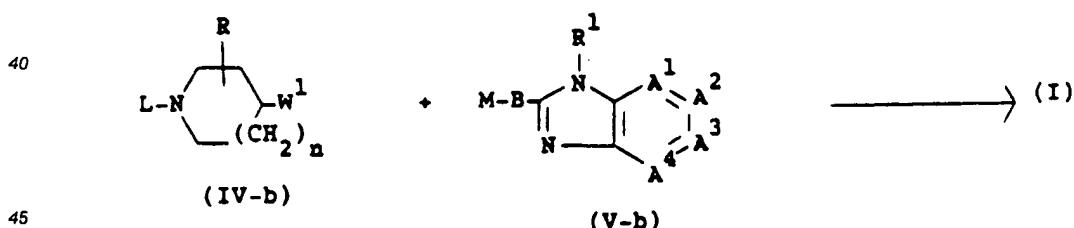
The compounds of formula (I) can also be prepared by reacting an intermediate of formula (V) with an intermediate of formula (IV) wherein E¹ and E² are selected so that during the reaction a radical -B- is formed.



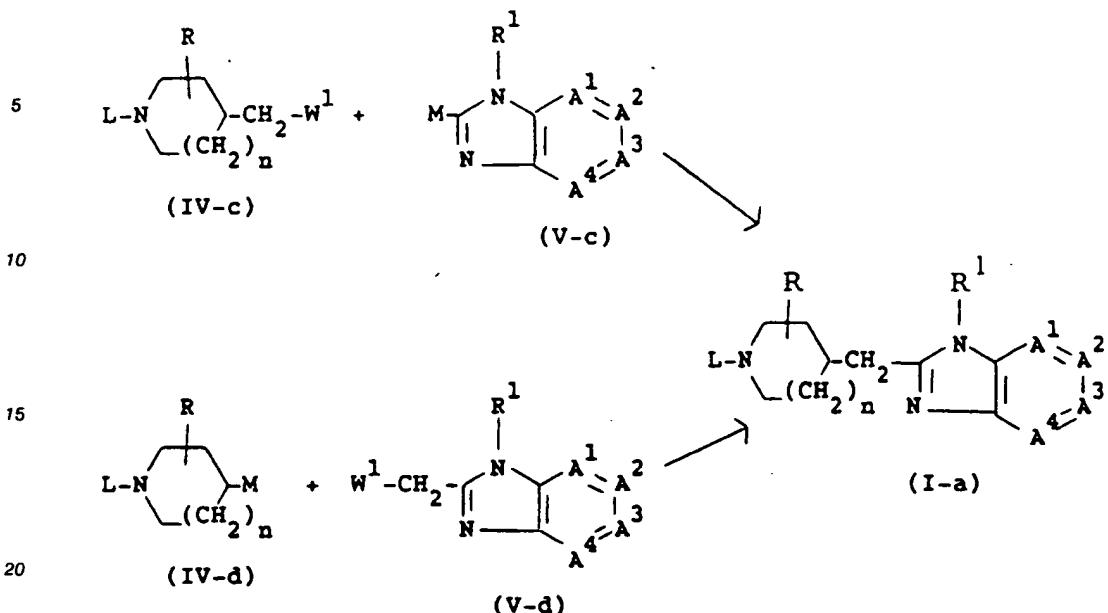
For example, the compounds of formula (I) can be prepared by reacting an intermediate of formula (IV) wherein E¹ is a radical of formula -B-M with an intermediate of formula (V) wherein E² is a radical of formula -W.



In (IV-a) M is, depending upon the nature of B, hydrogen or an appropriate alkali metal or earth alkaline metal and in (V-a) W has the previously described meanings. Additionally, the compounds of formula (I) can also be prepared by reacting an intermediate of formula (IV) wherein E¹ is W¹ with an intermediate of formula (V) wherein E² is a radical of formula -B-M, said W¹ and M having the previously described meanings.

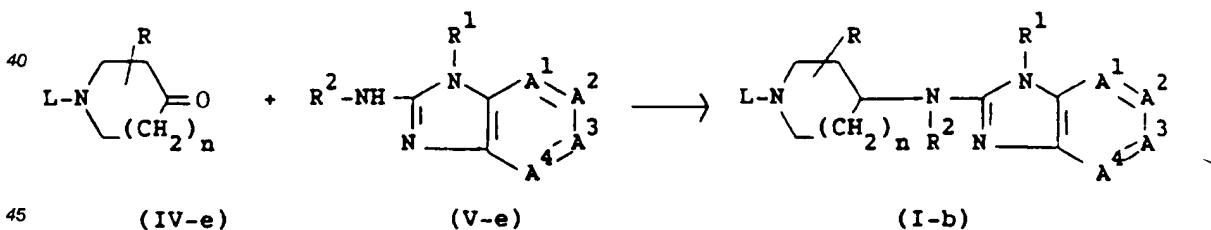


More particularly, the compounds of formula (I) wherein B is -CH₂- can also be prepared by reacting an intermediate of formula (IV) wherein E¹ represents a radical of formula -CH₂-W¹, (IV-c), with an intermediate of formula (V) wherein E² represents M, (V-c) or alternatively, by reacting an intermediate of formula (IV), wherein E¹ is a radical of formula -W¹, (IV-d), with an intermediate of formula (V) wherein E² is a radical of formula -CH₂-W¹, (V-d).



The reactions of (IV-a) with (V-a), (IV-b) with (V-b), (IV-c) with (V-c) and (IV-d) with (V-d) may conveniently be conducted in an appropriate solvent such as for example, an aromatic hydrocarbon, e.g., benzene, methylbenzene; an ether, e.g. 1,4-dioxane, 1,1'-oxybisethane, tetrahydrofuran; a halogenated hydrocarbon, e.g. trichloromethane; N,N-dimethylformamide; N,N-dimethylacetamide; nitrobenzene; dimethyl sulfoxide; 1-methyl-2-pyrrolidinone; and where M is hydrogen, said solvent may also be a C₁-6 alkanol, e.g., methanol, ethanol, 1-butanol; a ketone, e.g., 2-propanone, 4-methyl-2-pentanone. In some instances, the addition of an appropriate base such as, for example, an alkali metal carbonate or hydrogen carbonate, sodium hydride or an organic base such as, for example, N,N-diethylethanamine or N-(1-methylethyl)-2-propanamine and/or the addition of a iodide salt, preferably an alkali metal iodide, may be appropriate. Somewhat elevated temperatures may enhance the rate of the reaction.

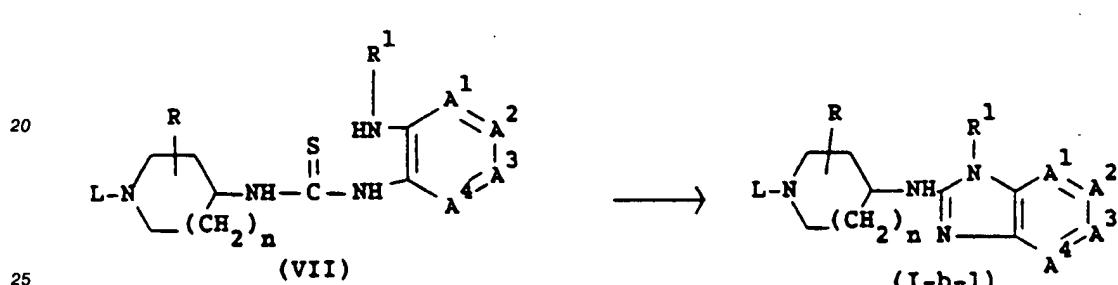
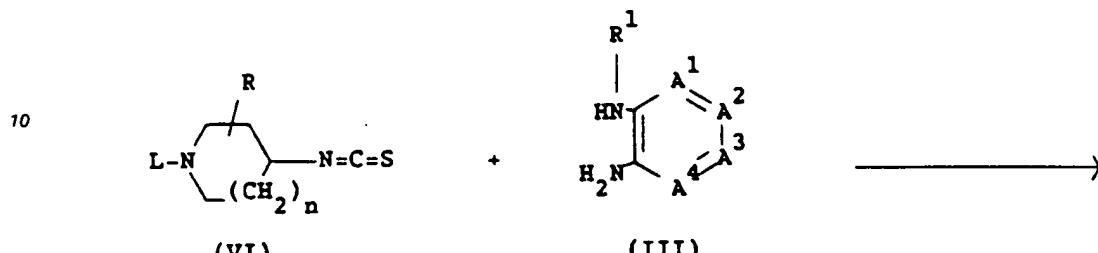
Or, the compounds of formula (I) wherein B is $-NR^2$ can also be prepared by reacting an intermediate of formula (IV) wherein E^1 is an oxo radical, (IV-e), with an intermediate of formula (V) wherein E^2 represents a radical $-NHR^2$, (V-e).



The reaction of (IV-e) with (V-e) is conveniently carried out by treating a mixture of the reactants in a suitable reaction-inert organic solvent with an appropriate reductant. Preferably, the 3-pyrrolidinone or hexahydro-1H-azepine-4-one of formula (IV-e) is first reacted with the benzimidazolamine of formula (V-e) to form an enamine, which optionally may be isolated and further purified, and subsequently subjecting the said enamine to a reduction reaction. Suitable solvents are, for example, water; C₁-6 alkanols, e.g. methanol, ethanol, 2-propanol; cyclic ethers, e.g. 1,4-dioxane; halogenated hydrocarbons, e.g. trichloromethane; N,N-dimethylformamide; N,N-dimethylacetamide; dimethyl sulfoxide; or a mixture of such solvents. Appropriate reductants are, for example, metal or complex metal hydrides, e.g. sodium borohydride, lithium aluminiumhydride; or hydrogen, the latter being preferably used in the presence of a suitable catalyst such as, for example, palladium-on-charcoal, platinum-on-charcoal. In order to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products it

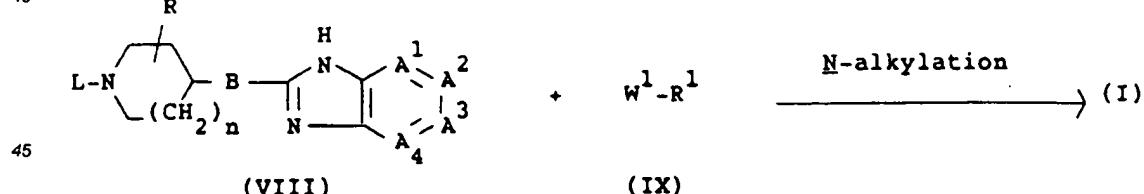
may be advantageous to add an appropriate catalyst-poison to the reaction mixture, e.g., thiophene.

The compounds of formula (I) wherein B is -NH- can also be prepared by a cyclodesulfurization reaction of an appropriate thiourea derivative of formula (VII), which may in situ be formed by condensing an isothiocyanate of formula (VI) with a diamine of formula (III).



Said cyclodesulfurization reaction may be carried out by the reaction of (VII) with an appropriate alkyl halide, preferably iodomethane in a suitable reaction-inert organic solvent, e.g., a C₁-₆ alkanol such as, 30 methanol, ethanol, 2-propanol. Otherwise, the cyclodesulfurization reaction may be carried out by the reaction of (VII) with an appropriate metal oxide or salt in an appropriate solvent according to art-known procedures. For example, the compounds of formula (I-b-1) can easily be prepared by the reaction of (VII) with a Hg(II) or Pb(II) oxide or salt such as, for example, HgO, HgCl₂, Hg(OAc)₂, PbO or Pb(OAc)₂. In certain instances it may be appropriate to supplement the reaction mixture with a small amount of sulfur. 35 Even so methanediiamines, especially dicyclohexylcarbodiimide may be used as cyclodesulfurizing agents.

The compounds of formula (I) can also be prepared by N-alkylating an intermediate of formula (VIII) with an appropriate reagent of formula (IX).

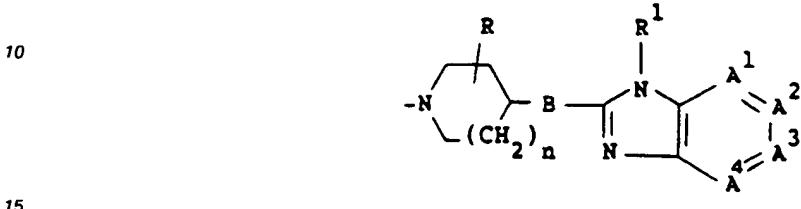


The N-alkylation reaction is conveniently conducted in an inert organic solvent such as, for example, an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene; an alkanol, e.g., methanol, ethanol, 1-butanol; a ketone, e.g., 2-propanone, 4-methyl-2-pentanone; an ether, e.g., 1,4-dioxane, 1,1'-oxybisethane, tetrahydrofuran; a polar aprotic solvent, e.g., N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, nitrobenzene, 1-methyl-2-pyrrolidinone. The addition of an appropriate base such as, for example, an alkali or an earth alkaline metal carbonate, hydrogen carbonate, hydroxide, and oxide, e.g., sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium hydroxide, calcium carbonate, calcium hydroxide, calcium oxide, or an organic base, such as, for example, a tertiary amine, e.g., N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, 4-ethylmorpholine may be utilized to pick up the acid which is liberated during the course of the reaction. In some instances the addition of a iodide salt,

preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures may enhance the rate of the reaction.

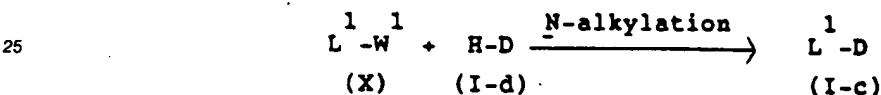
The compounds of formula (I) can also be converted into each other. Some examples of such conversions will be described hereinafter.

5 In order to simplify the structural representations of the compounds of formula (I) and of certain precursors and intermediates thereof the



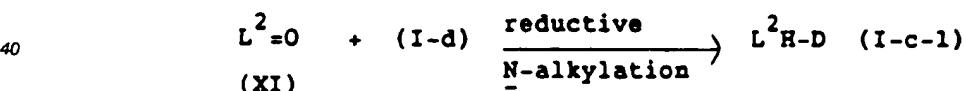
- radical will hereafter be represented by the symbol D.

20 The compounds of formula (I) wherein L is other than hydrogen, said L being represented by L¹, and said compounds being represented by formula (I-c) can generally be prepared by N-alkylating a compound of formula (I) wherein L is hydrogen, said compounds being represented by formula (I-d), with a reagent of formula (X).



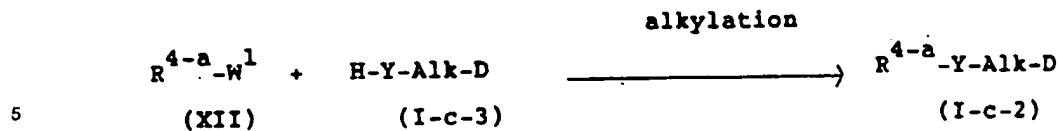
30 The said N-alkylation is conveniently carried out according to art-known N-alkylation procedures described hereinabove for the preparation of (I) starting from (VIII) and (IX).

35 The compounds of formula (I) wherein L is C₃₋₆cycloalkyl, C₁₋₁₂alkyl, a radical of formula (b-1), (b-2) or (b-3) said radical L being represented by the radical L²H-, and said compounds being represented by formula (I-c-1) can also be prepared by the reductive N-alkylation reaction of (I-d) with an appropriate ketone or aldehyde of formula L²=O (XI), said L²=O being an intermediate of formula L²H₂ wherein two geminal hydrogen atoms are replaced by =O, and L² is a geminal bivalent radical comprising C₃₋₆cycloalkylidene, C₁₋₁₂alkylidene, R³-C₁₋₆alkylidene and R⁵-Z²-C(=X)-Z¹-C₁₋₆alkylidene.



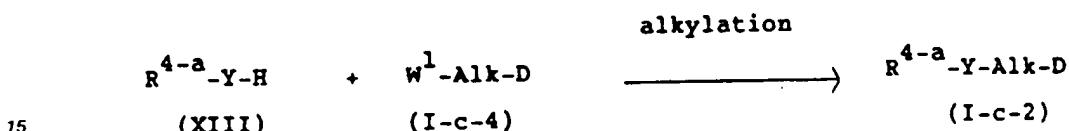
45 Said reductive N-alkylation reaction may conveniently be carried out by catalytically hydrogenating a stirred and heated mixture of the reactants in a suitable reaction inert organic solvent according to art-known catalytic hydrogenating procedures. Suitable solvents are, for example, water; alkanols, e.g., methanol, ethanol, 2-propanol; cyclic ethers, e.g., 1,4-dioxane; halogenated hydrocarbons, e.g., trichloromethane; N,N-dimethylformamide; dimethyl sulfoxide; or a mixture of two or more of such solvents. The term "art-known catalytic hydrogenating procedures" means that the reaction is carried out under hydrogen atmosphere in the presence of an appropriate catalyst such as, for example, palladium-on-charcoal, platinum-on-charcoal. In order to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products it may be advantageous to add an appropriate catalyst-poison to the reaction mixture, e.g., thiophene.

55 The compounds of formula (I) wherein L is a radical of formula (b-2) wherein R⁴ is Ar² or Het, said R⁴ being represented by R^{4-a} and said compounds by formula (I-c-2) may also be prepared by alkylating a compound of formula (I) wherein L is a radical of formula (b-2) wherein R⁴ is hydrogen, said compounds being represented by formula (I-c-3), with a reagent of formula (XII).



The compounds of formula (I-c-2) can also be prepared by alkylating a compound of formula (I-c-4) with a reagent of formula (XIII).

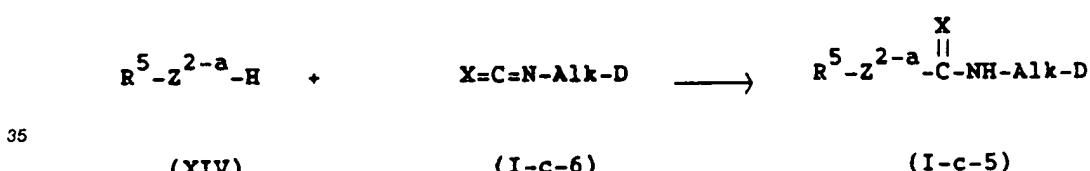
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The alkylation reactions of (XII) with (I-c-3) and (XIII) with (I-c-4) may conveniently be conducted in an inert organic solvent such as, for example, an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene; a ketone, e.g., 2-propanone, 4-methyl-2-pentanone; an ether, e.g., 1,4-dioxane, 1,1'-oxybisethane, tetrahydrofuran; and a polar aprotic solvent, e.g., N,N-dimethylformamide; N,N-dimethylacetamide; dimethyl sulfoxide; nitrobenzene; 1-methyl-2-pyrrolidinone. The addition of an appropriate base such as, for example, an alkali metal carbonate or hydrogen carbonate, sodium hydride or an organic base such as, for example, N,N-diethylethanamine or N-(1-methylethyl)-2-propanamine may be utilized to pick up the acid which is liberated during the course of the reaction. Somewhat elevated temperatures may enhance the rate of the reaction.

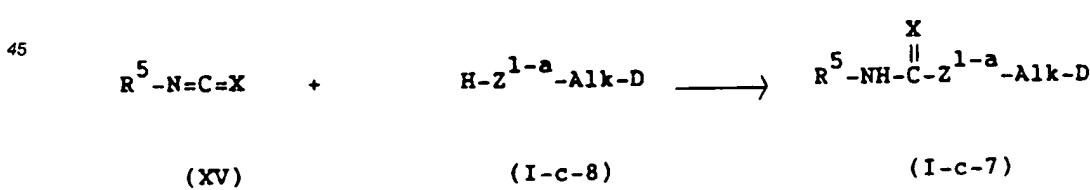
The compounds of formula (I) wherein L is a radical of formula (b-3) wherein Z¹ is NH and Z² is other than a direct bond, said Z² being represented by Z^{2-a}, and said compounds by (I-c-5) can be prepared by reacting an isocyanate or isothiocyanate of formula (I-c-6) with a reagent of formula (XIV).

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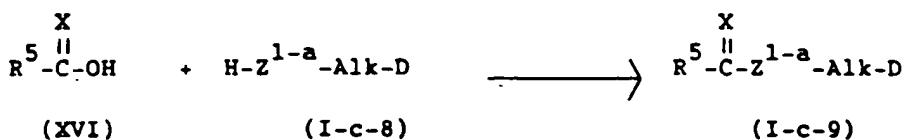
The compounds of formula (I) wherein L is a radical of formula (b-3) wherein Z² is NH and Z¹ is other than a direct bond, said Z¹ being represented by Z^{1-a} and said compounds by (I-c-7), can be prepared by reacting a isocyanate or isothiocyanate of formula (XV) with a compound of formula (I-c-8).

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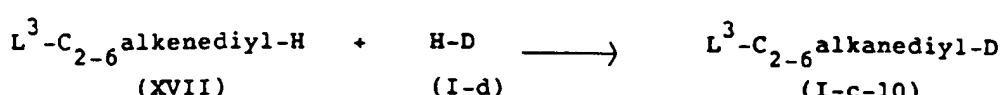
The reaction of (XIV) with (I-c-6), or (XV) with (I-c-8) is generally conducted in a suitable reaction-inert solvent such as, for example, an ether, e.g., tetrahydrofuran. Elevated temperatures may be suitable to enhance the rate of the reaction.

55 The compounds of formula (I) wherein L is a radical of formula (b-3) wherein Z² is a direct bond and Z¹ is other than a direct bond, said compounds being represented by (I-c-9), can be prepared by reacting a reagent of formula (XVI) or a functional derivative thereof with a compound of formula (I-c-8).



The reaction of (XVI) with (I-c-8) may generally be conducted following art-known esterification- or amidation reaction procedures. For example, the carboxylic acid may be converted into a reactive derivative, e.g., an anhydride or a carboxylic acid halide, which subsequently, is reacted with (I-c-8); or by reacting (XVI) and (I-c-8) with a suitable reagent capable of forming amides or esters, e.g., N,N-methanetetraylbis[cyclohexamine], 2-chloro-1-methylpyridinium iodide. Said reactions are most conveniently conducted in a suitable solvent such as, for example, an ether, e.g., tetrahydrofuran, a halogenated hydrocarbon, e.g., dichloromethane, trichloromethane or a polar aprotic solvent. The addition of a base such as, N,N-diethylethanamine may be appropriate.

The compounds of formula (I) wherein L is a radical of formula L^3-C_2-6 alkanediyl, said L^3 being Ar², Het, Ar²-sulfonyl or a radical of formula R⁵-Z²-C(=X)-, and said compounds being represented by formula (I-c-10), may also be prepared by reacting an appropriate alkenylene of formula (XVII) with a compound of formula (I-d).



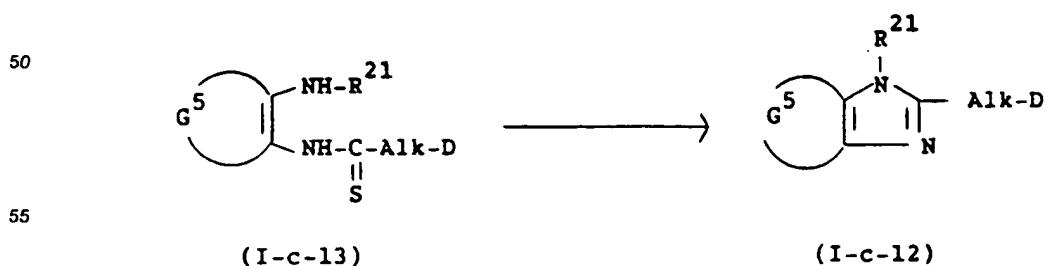
The compounds of formula (I) wherein L is a radical of formula (b-4) or a 2-hydroxyethyl, said compounds being represented by formula (I-c-11), may also be prepared by reacting a reagent (XVIII) with a compound of formula (I-d).



³⁵ R²⁴ in (XVIII) and (I-c-11) being hydrogen or a radical R⁶-O-CH₂-·. The reactions of (XVII) with (I-d) and (XVIII) with (I-d) may be conducted by stirring and, if desired, heating the reactants. The said reactions may be conducted in a suitable solvent such as, for example, a ketone, e.g., 2-propanone, 4-methyl-2-pentanone, an ether, e.g., tetrahydrofuran, 1,1'-oxybisethane, an alcohol, e.g., methanol, ethanol, 1-butanol, a polar aprotic solvent, e.g., N,N-dimethylformamide, N,N-dimethylacetamide.

The compounds of formula (I) wherein R³, R⁴ or R⁵ are Het, may also be prepared following procedures for preparing ring systems which are known in the art or analogues procedures thereof. A number of such cyclization procedures are described in for example, the Published European Patent Publication No. 151 826.

45 For example, compounds of formula (I-c-12) can be obtained by a cyclodesulfurization reaction of (I-c-13) following similar procedures as described for the preparation of (I-b-1) from (VII).



In (I-c-13) and (I-c-12) G⁵ and R²¹ have the same meanings as described hereinbefore.

The compounds of formula (I) can also be converted into each other following art-known procedures of functional group transformation. Some examples of such procedures will be cited hereinafter.

The compounds of formula (I), wherein -B- is -S-, may be converted into the corresponding compounds of formula (I), wherein -B- is -SO- or -SO₂- by an appropriate oxidation reaction, e.g., by reacting the former compounds with a suitable oxidizing agent such as, for example, potassium periodate, a peroxide, e.g. 3-chlorobenzenecarboxylic acid, hydrogen peroxide, in a suitable solvent such as, for example, an ether, e.g., tetrahydrofuran, 1,1'-oxybisethane, a hydrocarbon, e.g., benzene, a halogenated hydrocarbon, e.g., dichloromethane, trichloromethane. In the instance where a sulfinyl is desired, said oxidation reaction is preferably conducted at lower temperatures with approximately one equivalent of the oxidizing agent, while where a sulfonyl is desired, said oxidation reaction may be conducted at room or at an elevated temperature with an excess of oxidizing agent.

The compounds of formula (I) containing a cyano substituent can be converted into the corresponding amines by stirring and, if desired, heating the starting cyano compounds in a hydrogen containing medium in the presence of a suitable amount of an appropriate catalyst such as, for example, platinum-on-charcoal, Raney-nickel. Suitable solvents are, for example, methanol, ethanol.

The hydrogen atoms of the amino function(s) of compounds of formula (I) may be substituted following art-known procedures such as, for example, N-alkylation N-acylation, reductive N-alkylation. For example alkylcarbonyl, arylcarbonyl groups may be introduced by reacting the starting amine with an appropriate carboxylic acid or a derivative thereof such as, for example, an acid halide, acid anhydride.

The compounds of formula (I) containing a substituted amine may be converted into the corresponding compounds of formula (I) wherein said nitrogen bears a hydrogen atom following art-known methods for preparing NH group. For example, where said amine is substituted with a C₁-₆alkyloxycarbonyl group by treating the starting material with an acid or a base in a suitable solvent. As suitable acids there may be cited hydrohalic acids, e.g., hydrochloric acid or hydrobromic acid, sulfuric, phosphoric acid, preferably employed as an aqueous solution or mixed with, e.g., acetic acid. Suitable bases are the alkali metal hydroxides, hydrides or alkoxides in an aqueous or alcoholic medium. Or, where said nitrogen is substituted with an Ar²-CH₂ group, by treating the starting compounds with hydrogen in the presence of a suitable catalyst, e.g., palladium-on-charcoal, platinum-on-charcoal, preferably in an alcoholic medium.

The compounds of formula (I) containing a nitrogen atom substituted with Ar²-CH₂- may also be converted into the corresponding compounds where said nitrogen is substituted with C₁-₆alkyloxycarbonyl, for example by treating the former compounds with a C₁-₆alkylcarbonohalide, e.g., ethyl carbonochloride in the presence of a suitable solvent, e.g., methylbenzene and, if desired, in the presence of an appropriate base.

The compounds of formula (I) wherein the pyrrolidine or hexahydro-1H-azepine nitrogen is substituted with a C₁-₆alkyloxycarbonyl group may be converted into the corresponding compounds wherein the ring nitrogen is substituted with methyl by reducing the starting compounds with an appropriate reductant such as, lithium tetrahydroaluminate.

The compounds of formula (I) containing an amino group may be converted into the corresponding isothiocyanato containing compounds by treating the starting amino compounds with CS₂ optionally in the presence of N,N-methanetetrailbis[cyclohexamine].

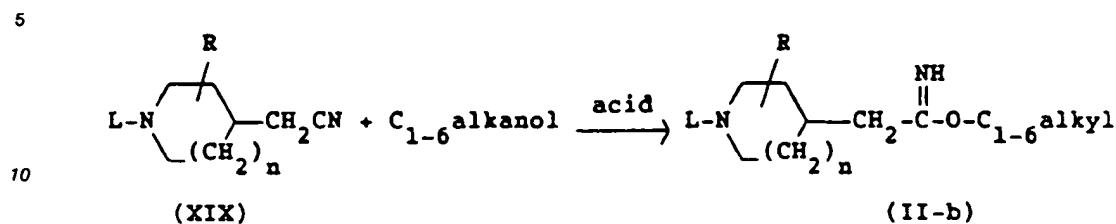
In all of the foregoing and in the following preparations, the reaction products may be isolated from the reaction mixture and, if necessary, further purified according to methodologies generally known in the art.

The compounds of formula (I) have basic properties and, consequently, they may be converted to their therapeutically active non-toxic acid addition salt forms by treatment with appropriate acids, such as, for example, inorganic acids, such as hydrohalic acid, e.g., hydrochloric, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic acid. Conversely the salt form can be converted by treatment with alkali into the free base form.

The compounds of formula (I) containing acidic protons may also be converted to their therapeutically active non-toxic metal or amine substitution salt forms by treatment with appropriate organic or inorganic bases.

Some intermediates and starting materials in the foregoing preparations are known compounds which may be prepared according to art-known methodologies of preparing said or similar compounds and others are new. A number of such preparation methods will be described hereinafter in more detail.

The intermediates of formula (II), wherein B is CH₂, X³ is NH and W is C₁₋₅alkyloxy, said intermediates being represented by the formula (II-b), can be prepared by reacting a (cyanomethyl)derivative of formula (XIX) with an alcohol, e.g., methanol, ethanol, in the presence of an acid, e.g., hydrochloric acid.



The intermediates of formula (IV) may be prepared by reduction of an appropriate 3-pyrrolidinone or hexahydro-1H-azepin-4-one, if desired, followed by an appropriate art-known groupstransformation procedure, for example, in the instance where a compound of formula (IV-b) is desired, by reacting the thus obtained alcohol with thionyl chloride, methylsulfonyl chloride in order to obtain an appropriate leaving group.

Starting materials such as intermediates of formulae (VI), (VIII), (X) and (XI) can conveniently be prepared following similar procedures as described in, for example, U.S. Pat. Nos. 4,219,559; 4,335,127; 4,342,870; 4,443,451; 4,634,704; 4,695,569 and 4,588,722.

From formula (I) it is evident that the compounds of this invention may have several asymmetric carbon atoms in their structure. Each of these chiral centers may be present in a R- and a S-configuration, this R- and S-notation being in correspondence with the rules described by R.S. Cahn, C. Ingold and V. Prelog in
 25 Angew. Chem., Int. Ed. Engl., 5, 385, (1966).

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereoisomers may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e.g., counter current distribution, and enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids.

Pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically.

It is evident that the cis and trans diastereomeric racemates may be further resolved into their optical isomers, cis(+), cis(-), trans(+) and trans(-) by the application of methodologies known to those skilled in the art.

Stereochemically isomeric forms of the compounds of formula (I) are naturally intended to be embraced within the scope of the invention.

The compounds of formula (I), the pharmaceutically acceptable acid addition salts and possible stereochemically isomeric forms thereof possess useful pharmacological properties. More particularly, they are active as anti-histaminics which activity can clearly be demonstrated by, e.g., the results obtained in the "Protection of Rats from Compound 48/80-induced lethality"-test, the "Histamine antagonism in Guinea Pig"-test and the "Ascaris Allergy test in Dogs"-test described in Arch. Int. Pharmacodyn. Ther. 251, 39-51 (1981). Apart from their anti-histaminic properties some of the subject compounds also show serotonin-antagonism.

Furthermore the compounds of formula (I), the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof are particularly attractive due to their favourable pharmacokinetical profile. In particular, some show a rapid onset so that their anti-histaminic effects are almost instantaneously present. Especially those compounds of formula (I) wherein n = 2 show an interesting pharmacokinetical profile due to their combined rapid onset and favourable limited duration of action.

In view of their anti-histaminic properties, the compounds of formula (I) and their acid addition salts are very useful in the treatment of allergic diseases such as, for example, allergic rhinitis, allergic conjunctivitis, chronic urticaria, and allergic asthma.

In view of their useful pharmacological properties the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These

pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils and alcohols in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; 5 or solid carriers such as starches, sugars, kaolin, lubricants, binders and disintegrating agents in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, 10 may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, and suspending agents may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a 15 significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. Acid addition salts of (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

20 It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including 25 scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and segregated multiples thereof.

The present invention is also related with a method of treating allergic diseases in warm-blooded animals suffering from said allergic diseases by administering an effective anti-allergic amount of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof.

30 Those of skill in treating allergic diseases in warm-blooded animals could easily determine the effective amount from the test results presented hereinafter. In general it is contemplated that an effective amount would be from 0.001 mg/kg to 100 mg/kg body weight, and more preferably from 0.01 mg/kg to 1 mg/kg body weight.

In the following examples, unless otherwise stated, all parts are by weight.

35

EXPERIMENTAL PART

A. Preparation of Intermediates

40 Example 1

a) A mixture of 180.0 parts of 2-chloro-3-nitropyridine, 122.0 parts of 2-thiophenemethanamine, 191.0 parts of sodium carbonate, 1 part of potassium iodide and 810 parts of N,N-dimethylacetamide was stirred for 1.50 hour at 100 °C. The reaction mixture was poured into a lot of water (about 4000 parts).
45 The whole was stirred overnight at room temperature. The precipitated product was filtered off and dried in vacuo at 40 °C, yielding 251.5 parts of 3-nitro-N-(2-thienylmethyl)-2-pyridinamine; mp. 100 °C (interm. 1).

50 A mixture of 125 parts of 3-nitro-N-(2-thienylmethyl)-2-pyridinamine and 560 parts of methanol, saturated with ammonia was hydrogenated at normal pressure and at room temperature with 10 parts of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was stirred overnight in 1,1'-oxybisethane. The product was filtered off and dried in vacuo at 40 °C, yielding 77 parts (70.8%) of N²-(2-thienylmethyl)-2,3-pyridinediamine; mp. 92.1 °C (interm. 2).

55 In a similar manner there were also prepared
N²-(2-furanyl methyl)-2,3-pyridinediamine as a residue (interm. 3);
N¹-[(5-methyl-2-furanyl)methyl]-1,2-benzenediamine as a residue (interm. 4); and
N²-[(5-methyl-2-furanyl)methyl]-2,3-pyridinediamine as a residue (interm. 5).

Example 2

a-1) To a stirred mixture of 25 parts of carbonothioic dichloride, 65 parts of water and 210 parts of trichloromethane were added dropwise 9.3 parts of ethyl 3-aminopyrrolidinecarboxylate. Upon completion, the reaction mixture was stirred for 15 minutes at room temperature. 10.7 Parts of calcium carbonate were added portionwise during a period of 10 minutes and stirring was continued overnight at room temperature. The reaction mixture was filtered and the separated organic layer was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using trichloromethane as eluent. The pure fractions were collected and the eluent was evaporated. The residue was distilled at 6.65 Pa, yielding 7.5 parts (69.3%) of ethyl 3-isothiocyanato-1-pyrrolidinecarboxylate; bp. 101 °C (interm 6).

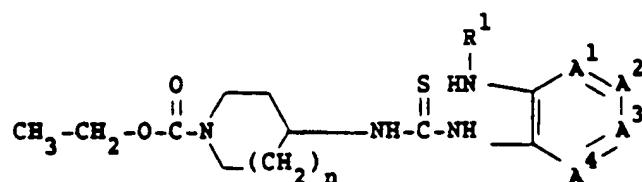
a-2) To 192 parts of cooled water were added portionwise 12.8 parts of sodium hydroxide. Upon complete addition, 25.3 parts of carbon disulfide were added and stirring was continued for 30 minutes at 10 °C. 55 Parts of ethyl 3-aminopyrrolidinecarboxylate were added and the whole was stirred for 30 minutes at 10 °C. 34.8 Parts of ethyl carbonochloridate were added dropwise (exothermic reaction) and stirring was continued for 4 hours at 60 °C. After cooling, the product was extracted with methylbenzene. The extract was washed twice with water, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of dichloromethane and ethanol (99:1 and 100:0.5 by volume) as eluents. The pure fractions were collected and the eluent was evaporated at a warm bath at 30 °C, yielding 25 parts (39.0%) of ethyl 3-isothiocyanato-1-pyrrolidinecarboxylate as a residue (interm. 6).

a-3) To a stirred and cooled (10 °C) mixture of 37 parts of N,N-methanetetrabisis[cyclohexanamine] and 594 parts of tetrahydrofuran were added 91.2 parts of carbon disulfide. After cooling to -10 °C, 27.5 parts of ethyl 3-aminopyrrolidinecarboxylate were added during a period of 5 minutes (exothermic reaction). The reaction mixture was allowed to reach room temperature and evaporated. The residue was purified by column chromatography over silica gel using trichloromethane as eluent. The pure fractions were collected and the eluent was evaporated, yielding 32 parts (99.8%) of ethyl 3-isothiocyanato-1-pyrrolidinecarboxylate as a residue (interm. 6).

a-4) A mixture of 8.6 parts of sodium hydroxide and 120 parts of water was stirred at a temperature below 10 °C and there were added successively 17 parts of carbon disulfide and 35 parts of ethyl 3-amino-1-pyrrolidinecarboxylate. Stirring was continued for 3 hours. Then there were added dropwise 23.5 parts of ethyl carbonochloridate. Upon completion, stirring was continued for 2 hours at 60 °C. The reaction mixture was extracted with methylbenzene. The extract was dried, filtered and evaporated, yielding 55 parts (100%) of ethyl 3-isothiocyanato-1-pyrrolidinecarboxylate as a residue (interm. 6).

b) A mixture of 80 parts of ethyl 3-isothiocyanato-1-pyrrolidinecarboxylate, 88.8 parts of N¹-[(5-methyl-2-furanyl)-methyl]-1,2-benzenediamine and 560 parts of tetrahydrofuran was stirred for 2 hours at reflux temperature. After cooling to room temperature, the reaction mixture was evaporated, yielding 144.9 parts (100%) of ethyl 3-[[[2-[(5-methyl-2-furanyl)methyl]amino]phenyl]amino]thioxomethyl]amino]-1-pyrrolidinecarboxylate as a residue (interm. 7).

In a similar manner there were also prepared:



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Int. No.	n	R ¹	A ¹ =A ² -A ³ =A ⁴	base/	mp(°C) salt
8	0	2-pyridinylmethyl	N=CH-CH=CH	HCl	190
9	0	2-thienylmethyl	N=CH-CH=CH	HCl	140
10	0	2-furanyl methyl	N=CH-CH=CH	base	residue
11	0	(5-methyl-2-furan- yl)methyl	N=CH-CH=CH	base	residue
12	2	(5-methyl-2-furan- yl)methyl	CH=CH-CH=CH	base	residue
13	2	(4-fluorophenyl)- methyl	N=CH-N=CH	base	residue
14	2	H	CH=CH-CH=CH	base	residue
15	2	(4-fluorophenyl)- methyl	CH=C(OCH ₃) ₂ -CH=CH	base	residue
16	2	(4-fluorophenyl)- methyl	CH=CH-N=CH	base	residue
17	2	(4-fluorophenyl)- methyl	CH=CH-C(OCH ₃) ₂ =CH	base	residue
18	2	(4-fluorophenyl)- methyl	CH=CH-CH=N	base	residue
19	2	(4-fluorophenyl)- methyl	CH=CH-C(CH ₃) ₂ =CH	base	residue
20	2	(5-methyl-2-furan- yl)methyl	CH=N-CH=CH	base	residue
21	2	H	CH=C(F)=C(F)=CH	base	residue

Example 3

a) A mixture of 15.8 parts of ethyl 3-amino-1-pyrrolidinecarboxylate, 18 parts of 1-isothiocyanato-2-nitrobenzene and 180 parts of tetrahydrofuran was stirred for 1 hour at room temperature. The reaction mixture was evaporated, yielding 34 parts (100%) of ethyl 3-[[[(2-nitrophenyl)-amino]thioxomethyl]amino]-2-pyrrolidinecarboxylate as a residue (int. 22).

b) A mixture of 34 parts of ethyl 3-[[[(2-nitrophenyl)amino]thioxomethyl] amino]-1-pyrrolidinecarboxylate, 56 parts of iron-powder, 2 parts of ammonium chloride, 160 parts of methanol and 30 parts of water was stirred and acidified with hydrochloric acid. Stirring was continued for 2 hours at reflux temperature. The reaction mixture was filtered over diatomaceous earth and the filtrate was evaporated, yielding 30 parts (97.5%) of ethyl 3-[[[(2-aminophenyl)amino]thioxomethyl]amino]-1-pyrrolidinecarboxylate as a residue (interm. 23).

Example 4

a) A mixture of 56 parts of ethyl hexahydro-4-oxo-1H-azepinecarboxylate, 40 parts of ethyl 2-cyanoacetate, 60 parts of N,N-diethylethanamine, 400 parts of methanol and 3 parts of thiophene in methanol 4% was hydrogenated at normal pressure and at room temperature with 4 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated, yielding 84.6 parts (99.8%) of ethyl α -cyano-1-(ethoxycarbonyl)hexahydro-1H-azepine-4-acetate as a residue (int. 24).

b) A mixture of 84.6 parts of ethyl α -cyano-1-(ethoxycarbonyl)hexahydro-1H-azepine-4-acetate, 300 parts of dimethyl sulfoxide and 15 parts of water was stirred and heated for 5 hours in an oil bath at 150°C while ethanol was distilled off. The excess of dimethyl sulfoxide was distilled off and the residue was taken up in water. The product was extracted with dichloromethane. The extract was washed with

water, dried, filtered and evaporated. The residue was distilled at 13.30 Pa, yielding 43.2 (66.5%) of ethyl 4-(cyanomethyl)hexahydro-1H-azepinecarboxylate; bp.125 °C (int. 25).

c) Through a stirred mixture of 21 parts of ethyl 4-(cyanomethyl)hexahydro-1H-azepinecarboxylate, 5.06 parts of ethanol and 97.5 parts of trichloromethane was bubbled gaseous hydrogen chloride. The whole was allowed to stand over weekend in an ice box and then evaporated, yielding 29.2 parts (100%) of ethyl 4-(2-ethoxy-2-iminoethyl)hexahydro-1H-azepine-1-carboxylate monohydrochloride (int. 26).

Example 5

a) A mixture of 46 parts of ethyl hexahydro-4-oxo-1H-azepine-1-carboxylate, 26 parts of benzenehexanamine, 2 parts of a solution of thiophene in methanol 4% and 400 parts of methanol was hydrogenated at normal pressure and at room temperature with 4 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated, yielding 69.1 parts (100%) of ethyl hexahydro-4-[(phenylmethyl)amino]-1H-azepine-1-carboxylate as a residue (interm. 27).

b) 69.1 Parts of ethyl hexahydro-4-[(phenylmethyl)amino]-1H-azepine-1-carboxylate were hydrogenated in the presence of a solution of thiophene in methanol at normal pressure and at room temperature with 4 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated, yielding 46.9 parts (100%) of ethyl 4-aminohexahydro-1H-azepine-1-carboxylate as a residue (interm. 28).

c) To a stirred and cooled(-10 °C) mixture of 63 parts of carbon disulfide, 52.1 parts of N,N'-methanetetracyl[2-cyclohexanamine] and 360 parts of tetrahydrofuran were added dropwise 46.9 parts of ethyl 4-aminohexahydro-1H-azepine-1-carboxylate. Upon complete addition, the reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was evaporated and the residue was stirred in 2,2'-oxybispropane. The precipitate was filtered off and the filtrate was evaporated, yielding 70.75 parts (100%) of ethyl hexahydro-4-isothiocyanato-1H-azepine-1-carboxylate as a residue (interm. 29).

d) A mixture of 119 parts of ethyl hexahydro-4-isothiocyanato-1H-azepine-1-carboxylate, 95.4 parts of N²-[(5-methyl-2-furanyl)methyl]-2,3-pyridinediamine and 810 parts of tetrahydrofuran was stirred for 6 hours at reflux temperature. After cooling, the reaction mixture was evaporated, yielding 203 parts (100.0%) of ethyl hexahydro-4-[[2-[(5-methyl-2-furanyl)methyl]amino]-3-pyridinyl]amino]-1H-azepine-1-carboxylate as a residue (interm. 30).

Example 6

To a stirred mixture of 23.5 parts of N-(4-fluorophenylmethyl)-1,2-benzenediamine and 14.4 parts of concentrated hydrochloric acid were added dropwise 9 parts of cyanamide at 100 °C. After stirring for 3 hours at 100 °C, there were added dropwise 10.5 parts of a sodium hydroxide solution 50%. Upon completion, stirring was continued overnight at reflux temperature. The reaction mixture was cooled and taken up in a mixture of water, trichloromethane and N,N-dimethylformamide. The organic phase was separated, dried, filtered and evaporated. The residue was stirred in trichloromethane. The product was filtered off and crystallized from trichloromethane, yielding 2.5 parts (9.5%) of 1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine ; mp. 189.5 °C (int. 31).

Example 7

A mixture of 47.5 parts of N²-(2-furanyl methyl)-2,3-pyridinediamine, 36.5 parts of methyl (iminomethoxymethyl)carbamate, 34.5 parts of acetic acid and 450 parts of methylbenzene was stirred and heated for 16 hours at 65~68 °C. The reaction mixture was evaporated. 140 Parts of potassium hydroxide, 50 parts of water and 400 parts of 2-propanol were added to the residue and stirring was continued for 16 hours at reflux. The reaction mixture was concentrated to 1/4 of its volume. 500 Parts of water were added and 2-propanol was distilled off azeotropically. After stirring for 1 hour at room temperature, the product was filtered off, washed successively twice with 20 parts of water and three times with 12 parts of 2-propanone and crystallized from 1,2-dichloroethane. The product was filtered off and dried in vacuo at 50 °C, yielding 27.3 parts (51.0%) of 3-(2-furanyl methyl)-3H-imidazo[4,5-b]pyridin-2-amine; mp. 193.3 °C (interm. 32).

In a similar manner there was also prepared:

1-(2-furanyl methyl)-1H-benzimidazol-2-amine as a residue (int. 33).

B. Preparation of Final compounds

Example 8

A mixture of 176.5 parts of ethyl 3-[[[2-[(4-thiazolylmethyl)-amino]-3-pyridinyl]amino]thioxomethyl]-amino]-1-pyrrolidinecarboxylate dihydrochloride, 163.0 parts of mercury(II) oxide, 0.1 parts of sulfur and 480 parts of methanol, saturated with ammonia was stirred for 1 hour at reflux temperature. The reaction mixture was filtered over diatomaceous earth while hot, washed with boiling methanol and the filtrate was evaporated. The residue was converted into the (E)-2-butenedioate salt in 1600 parts of 2-propanone. The salt was filtered off, washed with 2,2'-oxybispropane and dried in vacuo at 40 °C, yielding 157.0 parts (77.6%) of ethyl 3-[[3-(4-thiazolylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-pyrrolidinecarboxylate (E)-2-butenedioate(2:3); mp. 150 °C (compound 1).

In a similar manner there were also prepared ethyl 3-[[1H-benzimidazol-2-yl]amino]-1-pyrrolidinecarboxylate monohydrochloride as a residue (compound 2); ethyl 3-[[3-(2-pyridinylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-pyrrolidinecarboxylate as a residue (compound 3); ethyl 3-[[3-(2-thienylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-pyrrolidinecarboxylate as a residue (compound 4); ethyl 3-[[3-(2-furanyl) methyl]-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-pyrrolidinecarboxylate as a residue (compound 5); ethyl 3-[[3-[5-methyl-2-furanyl]methyl]-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-pyrrolidinecarboxylate as a residue (compound 6); ethyl 3-[[1-[(5-methyl-2-furanyl)methyl]-1H-benzimidazol-2-yl]amino]-1-pyrrolidinecarboxylate as a residue (compound 7); ethyl hexahydro-4-[[1-[(5-methyl-2-furanyl)methyl]-1H-benzimidazol-2-yl]amino]-1H-azepine-1-carboxylate as a residue (compound 8); and ethyl hexahydro-4-[[3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1H-azepine-1-carboxylate as a residue (compound 9).

Example 9

A mixture of 33.6 parts of ethyl 4-[[[(2-aminophenyl)amino]thioxomethyl]amino]hexahydro-1H-azepine-1-carboxylate, 26 parts of mercury(II) oxide, 0.1 parts of sulfur and 450 parts of tetrahydrofuran was stirred for 3 hours at reflux temperature. The reaction mixture was filtered while hot over diatomaceous earth and the filtrate was evaporated. The residue was boiled in acetonitrile. The product was filtered off and dried, yielding 24.5 parts (81.0%) of ethyl 4-[(1H-benzimidazol-2-yl-amino)hexahydro-1H-azepine-1-carboxylate; mp. 174.6 °C. (compound 10).

In a similar manner there were also prepared: ethyl 4-[[1-(4-fluorophenyl)methyl]-6-methoxy-1H-benzimidazol-2-yl]-amino]hexahydro-1H-azepine-1-carboxylate; mp. 157.6 °C (compound 11); ethyl 4-[[1-[(4-fluorophenyl)methyl]-1H-imidazo[4,5-c]pyridin-2-yl]-amino]hexahydro-1H-azepine-1-carboxylate as a residue (compound 12); ethyl 4-[[1-[(4-fluorophenyl)methyl]-5-methoxy-1H-benzimidazol-2-yl]-amino]hexahydro-1H-azepine-1-carboxylate as a residue (compound 13); ethyl hexahydro-4-[[3-[(5-methoxy-2-furanyl)methyl]-3H-imidazo[4,5-c]pyridin-2-yl]amino]-1H-azepine-1-carboxylate as a residue (compound 14); ethyl 4-[[1-[(4-fluorophenyl)methyl]-5-methyl-1H-benzimidazol-2-yl]-amino]hexahydro-1H-azepine-1-carboxylate as a residue (compound 15); and ethyl 4-[[5,6-difluoro-1H-benzimidazol-2-yl]amino]hexahydro-1H-azepine-1-carboxylate as a residue (compound 16).

Example 10

A mixture of 74 parts of ethyl 4-[[[4-[(4-fluorophenyl)methyl]-amino]-5-pyrimidinyl]amino]thioxomethyl]-amino]hexahydro-1H-azepine-1-carboxylate, 39 parts of mercury(II) oxide and 240 parts of ethanol was stirred for 1 hour at reflux temperature. The reaction mixture was filtered while hot over diatomaceous earth and the filtrate was evaporated. The residue was taken up in water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was crystallized from a mixture of 1,1'-oxybisethane and acetonitrile. The product was filtered off and dried, yielding 29 parts

(46.8%) of ethyl 4-[9-[(4-fluorophenyl)methyl]-9H-purin-8-yl]amino]hexahydro-1H-azepine-1-carboxylate; mp. 156.7 °C (compound 17).

In a similar manner there was also prepared:

5 ethyl 4-[1-[(4-fluorophenyl)methyl]-1H-imidazo[4,5-b]pyridin-2-yl]-amino]hexahydro-1H-azepine-1-carboxylate as a residue (compound 18).

Example 11

A mixture of 18.25 parts of ethyl 4-(2-ethoxy-2-iminoethyl)hexahydro-1H-azepine-1-carboxylate monohydrochloride, 10.15 parts of N²-[(5-methyl-2-furanyl)methyl]-2,3-pyridinediamine and 200 parts of methanol was stirred and refluxed for 48 hours. After evaporation, the residue was taken up in water and made alkaline with potassium carbonate. The product was extracted with methylbenzene. The extract was dried, filtered and evaporated, yielding 21.3 parts (100%) of ethyl hexahydro-4-[3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl]methyl]-1H-azepine-1-carboxylate as a residue (compound 19).

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Example 12

A mixture of 33.3 parts of ethyl hexahydro-4-oxo-1H-azepine-1-carboxylate, 36.15 parts of 1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine, 320 parts of methylbenzene and 0.1 parts of 4-methylbenzenesulfonic acid was stirred overnight at reflux temperature using a water separator. After cooling to 50 °C, 80 parts of ethanol were added. 4.2 Parts of sodium tetrahydroborate were added portionwise and upon completion, stirring was continued for 2 hours at 50 °C. After cooling, water and 4.8 parts of methanol were added while stirring. The layers were separated and the aqueous layer was extracted with methylbenzene. The combined organic layers were dried, filtered and evaporated, yielding 73 parts (100%) of ethyl 4-[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]hexahydro-1H-azepine-1-carboxylate as a residue (compound 20).

In a similar manner there was also prepared:

20 ethyl 4-[3-(2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl]amino]-hexahydro-1H-azepine-1-carboxylate as an oily residue (compound 21); and
25 ethyl 4-[1-(2-furanyl)methyl]-1H-benzimidazol-2-yl]amino]hexahydro-1H-azepine-1-carboxylate (E)-2-butenedioate(1:1); mp. 189.2 °C (compound 22).

Example 13

35 To a stirred mixture of 167 parts of ethyl 3-(1H-benzimidazol-2-yl-amino)-1-pyrrolidinecarboxylate and 2790 parts of N,N-dimethylacetamide were added portionwise 61.0 parts of a sodium hydride dispersion 50%. Upon completion, stirring was continued for 1 hour at 50 °C. 127.2 Parts of 2-(chloromethyl)pyridine hydrochloride were added portionwise at 80 °C. After complete addition, the whole was stirred for 2 hours at 80 °C. After cooling, the reaction mixture was poured into 1000 parts of water. The product was extracted twice with methylbenzene. The combined extracts were washed with water, dried, filtered and evaporated. The residue was purified twice by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 and 99:1 by volume) as eluents. The first and second fractions were collected and the eluent was evaporated. The residue was converted into the hydrochloride salt in 2-propanol and 2,2'-oxybispropane. The salt was filtered off and dried, yielding 69.5 (24%) parts of ethyl 3-[1-(2-pyridinylmethyl)-1H-benzimidazol-2-yl]amino]-1-pyrrolidinecarboxylate dihydrochloride; mp. >140 °C (compound 23).

In a similar manner there were also prepared:

40 ethyl 3-[1-(2-pyrazinylmethyl)-1H-benzimidazol-2-yl]amino]-1-pyrrolidinecarboxylate as a residue (compound 24);
45 1-[(2,4-dichlorophenyl)methyl]-N-(hexahydro-1-methyl-1H-azepin-4-yl)-1H-benzimidazol-2-amine; mp. 131.8 °C (compound 25); and
1-[(4-chlorophenyl)methyl]-N-(hexahydro-1-methyl-1H-azepin-4-yl)-1H-benzimidazol-2-amine; mp. 106.9 °C (compound 26).

55 Example 14

A mixture of 6 parts of ethyl 4-(1H-benzimidazol-2-ylamino)hexahydro-1H-azepine-1-carboxylate, 3.75 parts of 4-(chloromethyl)thiazole hydrochloride, 5.3 parts of sodium carbonate and 90 parts of N,N-

dimethylformamide was stirred overnight at 70 °C. Another amount of 4-(chloromethyl)thiazole hydrochloride and sodium carbonate were added and stirring was continued overnight at 70 °C. After cooling, the reaction mixture was poured into water. The product was extracted with methylbenzene. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the (E)-2-butenedioate salt in ethanol. The salt was filtered off and dried, yielding 1.4 parts (13.5%) of ethyl hexahydro-4-[[1-(4-thiazolylmethyl)-1H-benzimidazol-2-yl]amino]-1H-azepine-1-carboxylate (E)-2-butenedioate (1:1); mp. 143.7 °C (compound 27).

In a similar manner there were also prepared:

- 10 ethyl hexahydro-4-[[1-(phenylmethyl)-1H-benzimidazol-2-yl]amino]-1H-azepine-1-carboxylate as a residue (compound 28);
- 15 ethyl hexahydro-4-[[1-(2-thienylmethyl)-1H-benzimidazol-2-yl]amino]-1H-azepine-1-carboxylate as a residue (compound 29); and
- 20 ethyl 4-[[1-[bis(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-hexahydro-1H-azepine-1-carboxylate as a residue (compound 30).

In a similar manner there is also prepared:

ethyl hexahydro-4-[[1-(3-thienylmethyl)-1H-benzimidazol-2-yl]amino]-1H-azepine-1-carboxylate (compound 31).

20 Example 15

To a stirred mixture of 5.5 parts of ethyl 3-(1H-benzimidazol-2-yl-amino)-1-pyrrolidinecarboxylate, 6.4 parts of sodium carbonate, 0.1 parts of potassium iodide and 81 parts of N,N-dimethylacetamide were added portionwise 4.3 parts of 4-(chloromethyl)thiazole hydrochloride at 130 °C. Upon completion, stirring was continued for 3 hours at 130 °C. After cooling, the reaction mixture was poured into 450 parts of water. The product was extracted twice with methylbenzene. The combined extracts were washed with water, dried, filtered and evaporated, yielding 5.2 parts (69.9%) of ethyl 3-[[1-(4-thiazolylmethyl)-1H-benzimidazol-2-yl]amino]-1-pyrrolidinecarboxylate as an oily residue (compound 32).

In a similar manner there were also prepared:

- 30 ethyl 3-[[1-(2-thienylmethyl)-1H-benzimidazol-2-yl]amino]-1-pyrrolidinecarboxylate as an oily residue (compound 33); and
- 35 ethyl 4-[(1-ethyl-1H-benzimidazol-2-yl)amino]hexahydro-1H-azepine-1-carboxylate as a residue (compound 34).

35 Example 16

A mixture of 11 parts of ethyl 4-[[5,6-difluoro-1H-benzimidazol-2-yl]-amino]hexahydro-1H-azepine-1-carboxylate, 7.2 parts of 1-(chloromethyl)-4-fluorobenzene, 3.2 parts of sodium carbonate and 90 parts of N,N-dimethylformamide was stirred and heated for 24 hours at 80 °C. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using trichloromethane as eluent. The pure fractions were collected and the eluent was evaporated, yielding 6 parts (40.6%) of ethyl 4-[[5,6-difluoro-1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]hexahydro-1H-azepine-1-carboxylate as a residue; (compound 35).

In a similar manner there were also prepared:

- 45 ethyl 3-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-pyrrolidinecarboxylate as a residue (compound 36); and
- 50 ethyl hexahydro-4-[[1-(4-methylphenyl)methyl]-1H-benzimidazol-2-yl]-amino]-1H-azepine-1-carboxylate as a residue (compound 37).

Example 17

A mixture of 157.0 parts of ethyl 3-[[3-(4-thiazolylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-pyrrolidinecarboxylate (E)-2-butenedioate(2:3) and 870 parts of a hydrobromic acid solution 48% in water was stirred for 22 hours at 100 °C. After cooling, the precipitate was filtered off and washed with water. The filtrate was evaporated. The residue was taken up three times in methylbenzene and the solvent was evaporated each time. The oily residue was stirred in 2-propanone. The precipitate was filtered off and the filtrate was evaporated. The residue was taken up in boiling ethanol. The clear solution was filtered and the

filtrate was allowed to crystallize over weekend while stirring. The crystallized product was filtered off, washed with ethanol and dried in vacuo at 50 °C, yielding 106.5 parts (79.4%) of N-(3-pyrrolidinyl)-3-(4-thiazolylmethyl)-3H-imidazo[4,5-b]pyridin-2-amine dihydrobromide; mp. 260.5 °C (compound 38).

In a similar manner there were also prepared:

- 5 1-[(4-fluorophenyl)methyl]-N-(3-pyrrolidinyl)-1H-benzimidazol-2-amine as a residue (compound 39);
N-(3-pyrrolidinyl)-1-(4-thiazolylmethyl)-1H-benzimidazol-2-amine dihydrobromide hemihydrate; mp. 214.7 °C (compound 40);
1-[(2-pyrazinyl)methyl]-N-(3-pyrrolidinyl)-1H-benzimidazol-2-amine as a residue (compound 41);
1-(2-pyridinylmethyl)-N-(3-pyrrolidinyl)-1H-benzimidazol-2-amine dihydrochloride; mp. >260 °C (compound 42);
3-(2-pyridinylmethyl)-N-(3-pyrrolidinyl)-3H-imidazo[4,5-b]pyridin-2-amine trihydrobromide; mp. 253.5 °C (compound 43);
1-[(4-fluorophenyl)methyl]-N-(hexahydro-1H-azepin-4-yl)-1H-benzimidazol-2-amine dihydrochloride; mp. 193.3 °C (compound 44);
75 9-[(4-fluorophenyl)methyl]-N-(hexahydro-1H-azepin-4-yl)-9H-purin-8-amine dihydrochloride, hemihydrate; mp. 240.0 °C (compound 45);
1-[(4-fluorophenyl)methyl]-N-(hexahydro-1H-azepin-4-yl)-1H-imidazo[4,5-c]pyridin-2-amine; mp. 203.0 °C (compound 46); and
20 1-[(4-fluorophenyl)methyl]-N-(hexahydro-1H-azepin-4-yl)-1H-imidazo[4,5-b]pyridin-2-amine monohydrochloride; mp. 212.6 °C (compound 47).

Example 18

A mixture of 188 parts of ethyl hexahydro-4-[[1-[(5-methyl-2-furanyl)methyl]-1H-benzimidazol-2-yl]-amino]-1H-azepine-1-carboxylate, 166.5 parts of potassium hydroxide, 18 parts of water and 1440 parts of 2-propanone was stirred for 18 hours at reflux temperature. After cooling, another portion of 166.5 parts of potassium hydroxide was added and stirring was continued for 6 hours at reflux. After cooling, the reaction mixture was evaporated and the residue was stirred in 1500 parts of water. The product was extracted three times with dichlormethane. The extract was dried, filtered and evaporated. The residue was converted into the (E)-2-butenedioate salt in 2000 parts of 2-propanone and 800 parts of ethanol. The reaction mixture was allowed to cool while stirring. The precipitated product was filtered off, washed with 2-propanone and crystallized from a mixture of 2-propanone and ethanol (1:2 by volume). The product was filtered off, washed with 2-propanone and dried in vacuo at 50 °C, yielding 132.6 parts (52.9%) of N-(hexahydro-1H-azepin-4-yl)-1-[(5-methyl-2-furanyl)methyl]-1H-benzimidazol-2-amine (E)-2-butenedioate(2:3).trihydrate; mp. 115.2 °C (compound 48).

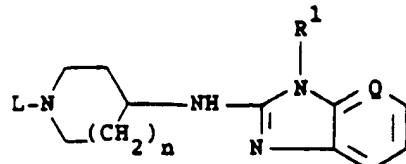
In a similar manner there were also prepared:

- 3-(2-furanylmethyl)-N-(hexahydro-1H-azepin-4-yl)-3H-imidazo[4,5-b]pyridin-2-amine dihydrochloride; mp. 253.1 °C (compound 49);
40 N-(hexahydro-1H-azepin-4-yl)-3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-amine ethanedioate(1:2); mp. 140 °C (compound 50);
N-(hexahydro-1H-azepin-4-yl)-3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-c]pyridin-2-amine (E)-2-butenedioate (2:5) hemihydrate; mp. 141.4 °C (compound 51);
2-[(hexahydro-1H-azepin-4-yl)methyl]-3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridine (E)-2-butenedioate (2:3) monohydrate; mp. 130.6 °C (compound 52);
45 N-(3-pyrrolidinyl)-1-(2-thienylmethyl)-1H-benzimidazol-2-amine as a residue (compound 53);
N-(3-pyrrolidinyl)-3-(2-thienylmethyl)-3H-imidazo[4,5-b]pyridin-2-amine dihydrochloride; mp. 140 °C (compound 54);
3-(2-furanylmethyl)-N-(3-pyrrolidinyl)-3H-imidazo[4,5-b]pyridin-2-amine (E)-2-butenedioate(2:3); mp.. 170 °C (compound 55);
50 3-(2-furanylmethyl)-N-(3-pyrrolidinyl)-3H-imidazo[4,5-b]pyridin-2-amine dihydrochloride, 2-propanolate(2:1) mp. >300 °C (compound 56);
3-[(5-methyl-2-furanyl)methyl]-N-(3-pyrrolidinyl)-3H-imidazo[4,5-b]pyridin-2-amine ethanedioate(1:2) as a residue (compound 57); and
1-[(5-methyl-2-furanyl)methyl]-N-(3-pyrrolidinyl)-1H-benzimidazol-2-amine monohydrochloride; mp. 190 °C (compound 58).

Example 19

A mixture of 4.2 parts of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one monohydrochloride, 6.9 parts of N-(3-pyrrolidinyl)-1-(4-thiazolylmethyl)-1H-benzimidazol-2-amine dihydrobromide, 9.7 parts of sodium carbonate, 0.1 parts of potassium iodide and 90 parts of N,N-dimethylacetamide was stirred for 1.5 hour at 100°C. After cooling, the reaction mixture was poured into 500 parts of water. The product was extracted three times with dichloromethane. The combined extracts were washed with water, dried, filtered and evaporated. The oily residue was converted into the (E)-2-butenedioate salt in 180 parts of 2-propanone and ethanol. The salt was filtered off and dried, yielding 6 parts (51.2%) of 6,7,8,9-tetrahydro-2-methyl-3-[2-[3-[(1-(4-thiazolylmethyl)-1H-benzimidazol-2-yl)amino]-1-pyrrolidinyl]ethyl]-4H-pyrido[1,2-a]pyrimidin-4-one (E)-2-butenedioate(2:5); mp. 148.1°C (compound 59).

10 In a similar manner there were also prepared:



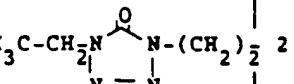
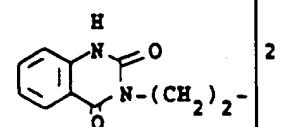
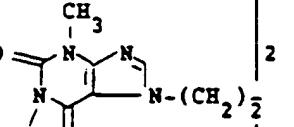
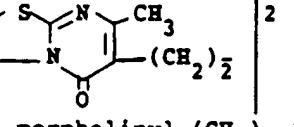
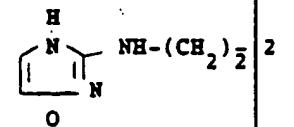
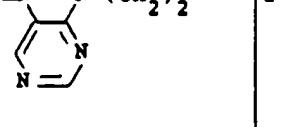
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No.	L	n	R¹	Q	salt base	mp. (°C)
25	60 4-CH ₃ O-C ₆ H ₄ -(CH ₂) ₂	0	2-pyridinylmethyl	CH	*	174.4
61 4-CH ₃ O-C ₆ H ₄ -(CH ₂) ₂	0	2-pyridinylmethyl	N	2(COOH) ₂ 0.5 H ₂ O	156.5	
30	62 4-CH ₃ O-C ₆ H ₄ -(CH ₂) ₂	0	2-thienylmethyl	CH	2(COOH) ₂	192.6
63 CH ₃ -CH ₂ -O-	0	2-thienylmethyl	CH	2(COOH) ₂	170	
C(=O)-NH-(CH ₂) ₂ -						
35	64 4-CH ₃ O-C ₆ H ₄ -(CH ₂) ₂	0	5-methyl-2-furanyl methyl	N	2(COOH) ₂	160.0
65 4-CH ₃ O-C ₆ H ₄ -(CH ₂) ₂	0	4-thiazolylmethyl	N	2(COOH) ₂	173.1	
40	66 4-CH ₃ O-C ₆ H ₄ -(CH ₂) ₂	2	4-F-C ₆ H ₄ -CH ₂ -	CH	2(COOH) ₂	192.3

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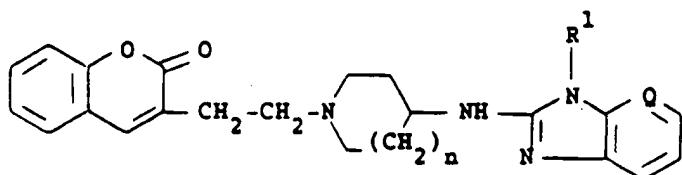
No.	L	n	R ¹	Q	salt base	mp. (°C)
5						
67	4-CH ₃ O-C ₆ H ₄ -(CH ₂) ₂	2	5-methyl-2-furanylmethyl	CH	1.5(COOH) ₂ 0.5 H ₂ O	121.5
10	4-CH ₃ O-C ₆ H ₄ -(CH ₂) ₂	2	5-methyl-2-furanylmethyl	N	2(COOH) ₂	120.2
15		2	5-methyl-2-furanylmethyl	N	**	113.9
70	C ₂ H ₅ -O-(CH ₂) ₂ -	2	5-methyl-2-furanylmethyl	N	2(COOH) ₂	110.2
71	2-thienyl-(CH ₂) ₂ -	2	5-methyl-2-furanylmethyl	N	2(COOH) ₂	179.0
20	2-pyridinyl-(CH ₂) ₂ -	2	5-methyl-2-furanylmethyl	N		-
25	4-F-C ₆ H ₄ -C-(CH ₂) ₃ -	2	5-methyl-2-furanylmethyl	N	2(COOH) ₂	153.2
30		2	5-methyl-2-furanylmethyl	N		-
35		2	5-methyl-2-furanylmethyl	N		-
40		2	5-methyl-2-furanylmethyl	N	3HCl.2H ₂ O	206.5
45	4-morpholinyl-(CH ₂) ₂ -	2	5-methyl-2-furanylmethyl	N		-
50		2	5-methyl-2-furanylmethyl	N		-
		2	5-methyl-2-furanylmethyl	N		-

No.	L	n	R ¹	Q	salt bas	mp. (°C)
80		2	5-methyl-2-furanylmethyl	N		-
81		2	5-methyl-2-furanylmethyl	N		-
82		2	5-methyl-2-furanylmethyl	N		-
83		2	5-methyl-2-furanylmethyl	N		-

* = (E)-2-butenedioate(2:5)

** = (E)-2-butenedioate(3:2) 2-propanolate(1:1)

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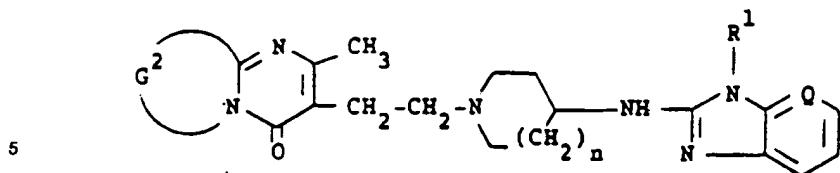


Comp. No.	n	R ¹	Q	salt/ base	mp. (°C)
84	0	4-thiazolylmethyl	CH	*	207.2
85	0	2-pyridinylmethyl	CH	* 0.5 H ₂ O	208.0
86	0	2-pyridinylmethyl	N	2 HNO ₃	160.3
87	0	2-thienylmethyl	CH	2 (COOH) ₂	196.4
88	0	4-thiazolylmethyl	N	2 (COOH) ₂	193.2
89	2	4-F-C ₆ H ₄ -CH ₂ -	CH	2 (COOH) ₂ /0.5 H ₂ O	194.3

* = (E)-2-butenedioate(2:3)

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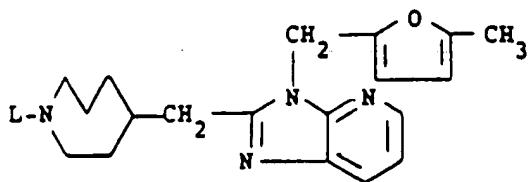


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No.	G ²	n	R ¹	Q	salt/ base	mp. (°C)
90	CH=CH-CH=CH	0	4-thiazolylmethyl	CH	(E)-2-butenedioate(2:3) 0.5 H ₂ O	204.8
91	CH=CH-CH=CH	0	2-pyridinylmethyl	CH	(E)-2-butenedioate(2:3)	198.0
92	CH=CH-CH=CH	0	2-pyridinylmethyl	N	4HCl 0.5 CH ₃ -CH(OH)-CH ₃	284.2
93	CH=CH-CH=CH	0	2-thienylmethyl	CH	(E)-2-butenedioate(1:3)	147.9
94	CH=CH-CH=CH	0	5-methyl-2-furanyl methyl	N	base	168.0
95	CH=CH-CH=CH	0	4-thiazolylmethyl	N	(E)-2-butenedioate(2:3)	214.9
96	CH=CH-CH=CH	0	5-methyl-2-furanyl methyl	CH	(E)-2-butenedioate(2:3)	205.8
97	(CH ₂) ₄	0	2-pyridinylmethyl	CH	(E)-2-butenedioate(2:3)	200.9
98	(CH ₂) ₄	0	2-thienylmethyl	CH	(E)-2-butenedioate(1:2)	157.3
99	(CH ₂) ₄	0	2-pyridinylmethyl	N	base	152.2
100	(CH ₂) ₄	0	5-methyl-2-furanyl methyl	N	(E)-2-butenedioate(2:3)	191.6
101	(CH ₂) ₄	0	4-thiazolylmethyl	N	(E)-2-butenedioate(2:3)	201.3
102	(CH ₂) ₄	0	5-methyl-2-furanyl methyl	CH	(E)-2-butenedioate(2:3)	177.0
103	CH=CH-CH=CH	2	5-methyl-2-furanyl methyl	CH	2 (COOH) ₂ /H ₂ O	134.2

45 6-[2-[hexahydro-4-[(3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl)amino]-1H-azepin-1-yl]-ethyl]-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one ethanedioate (1:2); mp. 136.0 °C (compound 104); and
and N-[1-(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]hexahydro-1H-azepin-4-yl]-3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-amine (E)-2-butenedioate(1:2) (compound 105);

In a similar manner there are also prepared:



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Comp. No.	L	B	base/ salt	mp. (°C)
106	$4-\text{CH}_3\text{O}-\text{C}_6\text{H}_4-(\text{CH}_2)_2-$	CH_2		
107		CH_2	(E)-2-butene-dioate(1:1)	188.4
108		CH_2		

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Example 20

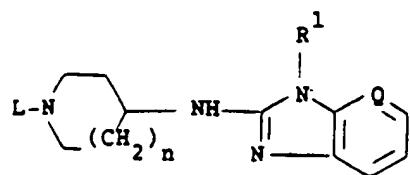
A mixture of 3.8 parts of 3-(2-bromoethyl)-2H-1-benzopyran-2-one, 4.7 parts of 3-(2-furanyl methyl)-N-(hexahydro-1H-azepin-4-yl)-3H-imidazo[4,5-b]pyridin-2-amine, 1.5 parts of sodium carbonate and 45 parts of N,N-dimethylacetamide was stirred for 48 hours at 80 °C. After cooling, the reaction mixture was poured into water and the product was extracted with trichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol, saturated with ammonia, (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the ethanedioate salt in ethanol. The salt was filtered off and dried, yielding 1 part (10%) of 3-[2-[4-[[3-(2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl]amino]hexahydro-1H-azepin-1-yl]ethyl]-2H-1-benzopyran-2-one ethanedioate(1:2); mp. 179.7 °C (compound 109).

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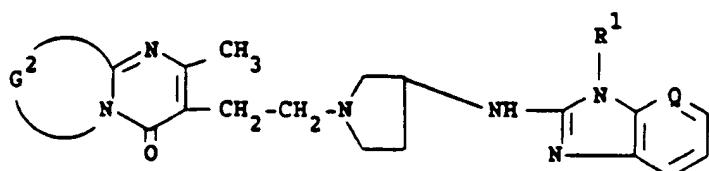
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No.	L	n	R ¹	Q	salt/ base	mp. (°C)
110	4-CH ₃ O-C ₆ H ₄ -(CH ₂) ₂ -O-	0	2-thienylmethyl	N	(E)-2-butene-dioate(1:1)	190.4
111	4-CH ₃ O-C ₆ H ₄ -(CH ₂) ₂ -O-	2	2-furanyl methyl	N	2 (COOH) ₂	158.2
112	2-oxo-2H-1-benzo-pyran-3-ylethyl	0	2-furanyl methyl	N	(E)-2-butene-dioate(2:1)	169.4
113	2-oxo-2H-1-benzo-pyran-3-ylethyl	0	2-thienylmethyl	N	(E)-2-butene-dioate(1:1)	202.4

25



35

No.	G ²	R ¹	Q	salt/ base	mp. (°C)
114	CH=CH-CH=CH	4-F-C ₆ H ₄ -CH ₂ -	CH	(E)-2-butenedioate(1:2) 2-propanol(2:1)	180.0
115	CH=CH-CH=CH	2-furanyl methyl	N	(E)-2-butenedioate(2:3)	190.0
116	CH=CH-CH=CH	2-thienyl methyl	N	(E)-2-butenedioate(2:3)	227.4
117	(CH ₂) ₄	2-furanyl methyl	N	(E)-2-butenedioate(2:3)	210.5
118	(CH ₂) ₄	2-thienyl methyl	N	(E)-2-butenedioate(2:3)	221.2
119	(CH ₂) ₄	2-furanyl methyl	N	(E)-2-butenedioate(1:3)	164.7

55 and 3-[2-[4-[(9-[(4-fluorophenyl)methyl]-9H-purin-8-yl]amino]hexahydro-1H-azepin-1-yl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (E)-2-butenedioate(1:2); mp. 210.5 °C (compound 120).

Example 21

A mixture of 3.1 parts of 1-(2-chloroethyl)-4-methoxybenzene, 6.9 parts of N-(3-pyrrolidinyl)-1-(4-thiazolylmethyl)-1H-benzimidazol-2-amine dihydrobromide, hemihydrate, 8.0 parts of sodium carbonate, 0.1 parts of potassium iodide and 120 parts of 4-methyl-2-pentanone was stirred for 22 hours at reflux temperature using a water separator. After cooling, the reaction mixture was poured into water. The organic phase was separated, washed with water, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane, methanol and ammonium hydroxide (95:5:0.5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the ethanedioate salt in 2-propanone. After cooling, the precipitated product was filtered off and dried, yielding 2.0 parts (21.7%) of N-[1-[2-(4-methoxyphenyl)ethyl]-3-pyrrolidinyl]-1-(4-thiazolylmethyl)-1H-benzimidazol-2-amine ethanedioate(1:2); mp. 191.1 °C (compound 121).

In a similar manner there were also prepared

3-[2-[3-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-pyrrolidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (E)-2-butenedioate(2:3), monohydrate; mp. 153.9 °C (compound 122);
 N[1-[2-(4-methoxyphenyl)ethyl]-3-pyrrolidinyl]-1-(2-pyrazinylmethyl)-1H-benzimidazol-2-amine ethanedioate(1:2); mp. 193.3 °C (compound 123); and
 N[1-[2-(4-methoxyphenyl)ethyl]-3-pyrrolidinyl]-1-[(5-methyl-2-furanyl)methyl]-1H-benzimidazol-2-amine ethanedioate(1:2); mp. 177.0 °C (compound 124).

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Example 22

A mixture of 6.2 parts of 1-[(4-fluorophenyl)methyl]-N-(3-pyrrolidinyl)-1H-benzimidazol-2-amine, 4.3 parts of sodium carbonate and 120 parts of 4-methyl-2-pentanone was stirred and refluxed for 30 minutes using a water separator. 4.9 Parts of 1-(2-chloroethyl)-1,3-dihydro-2H-benzimidazol-2-one were added at reflux temperature and stirring was continued for 20 hours at reflux temperature using a water separator. After cooling, the salts were filtered off and the filtrate was washed with water, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane, methanol and ammonium hydroxide (90:9:1 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the ethanedioate salt in 2-propanone. The salt was filtered off and dried in a dry pistol with methylbenzene, yielding 6.30 parts (45%) of 1-[2-[3-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-pyrrolidinyl]ethyl]-1,3-dihydro-2H-benzimidazol-2-one ethanedioate(2:5); mp. 190.6 °C (compound 125).

In a similar manner there was also prepared:

3-[2-[3-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-pyrrolidinyl]ethyl]-2H-1-benzopyran-2-one ethanedioate(1:2); mp. 208.1 °C (compound 126).

Example 23

40 A mixture of 1.85 parts of (2-bromoethyl)benzene, 3.1 parts of 1-[(4-fluorophenyl)methyl]-N-(3-pyrrolidinyl)-1H-benzimidazol-2-amine, 1.06 parts of sodium carbonate, 0.1 parts of potassium iodide and 120 parts of N,N-dimethylformamide was stirred and heated overnight at 70 °C. The reaction mixture was poured into water and the product was extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (96:4 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 2,2'-oxybispropane. The product was filtered off and dried, yielding 0.5 parts (12%) of 1-[(4-fluorophenyl)methyl]-N-[1-(2-phenylethyl)-3-pyrrolidinyl]-1H-benzimidazol-2-amine; mp. 126.1 °C (compound 127).

In a similar manner there were also prepared:

50 1-[(4-fluorophenyl)methyl]-N-[1-(3-phenoxypropyl)-3-pyrrolidinyl]-1H-benzimidazol-2-amine; mp. 104.7 °C (compound 128); and
 1-[(4-fluorophenyl)methyl]-N-[1-[2-(4-methoxyphenyl)ethyl]-3-pyrrolidinyl]-1H-benzimidazol-2-amine; mp. 143.8 °C (compound 129).

55 Example 24

A mixture of 7.6 parts of 3-(2-bromoethyl)-2H-1-benzopyran-2-one, 6.0 parts of 3-[(5-methyl-2-furanyl)methyl]-N-(3-pyrrolidinyl)-3H-imidazo-[4,5-b]pyridin-2-amine, 8.4 parts of sodium hydrogen carbonate, 0.1

parts of potassium iodide and 160 parts of ethanol was stirred for 4 hours at reflux temperature. After cooling to room temperature, the precipitate product was filtered off and the filtrate was evaporated. The residue was stirred in ethyl acetate. The precipitate was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane, hexane, 5 methanol and ammonium hydroxide (45:45:9:1 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the (E)-2-butenedioate salt in 2-propanone. The salt was filtered off and crystallized twice from ethanol. The product was filtered off, washed with ethanol and dried in vacuo at 50 °C, yielding 3 parts (25.6%) of 3-[2-[3-[3-[(5-methyl-2-furanyl) methyl]-3H-imidazo-[4,5-b]pyridin-2-yl]amino]-1-pyrrolidinyl]ethyl]-2H-1-benzopyran-2-one (E)-2-butenedioate(1:1); mp. 194.2 °C (compound 130).

In a similar manner there were also prepared:

3-[2-[3-[1-(2-pyrazinylmethyl)-1H-benzimidazol-2-yl]amino]-1-pyrrolidinyl]ethyl]-2H-1-benzopyran-2-one (E)-2-butenedioate(2:3).hemihydrate; mp. 204.7 °C (compound 131); and
2-methyl-3-[2-[3-[1-(2-pyrazinylmethyl)-1H-benzimidazol-2-yl]amino]-1-pyrrolidinyl]ethyl]-4H-pyrido[1,2-a]-
15 pyrimidin-4-one (E)-2-butenedioate(2:5); mp. 151.9 °C (compound 132).

Example 25

To a stirred and heated (60 °C) suspension of 14 parts of 1-(2-pyridinylmethyl)-N-(3-pyrrolidinyl)-1H-benzimidazol-2-amine dihydrochloride and 9.5 parts of sodium carbonate in 113 parts of N,N-dimethylformamide were added dropwise 3.2 parts of 2-chloroacetonitrile. Upon completion, stirring was continued for 3 hours at 60 °C. After cooling, the mixture was poured into ice water and the product was extracted six times with methylbenzene. The combined organic layers were washed with water, dried, filtered and evaporated, yielding 11 parts (87%) of 3-[1-(2-pyridinylmethyl)-1H-benzimidazol-2-yl]amino]-1-pyrrolidineacetonitrile as a residue (compound 133).

In a similar manner there were also prepared:

3-[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-pyrrolidineacetonitrile as a residue (compound 134);
3-[1-(2-pyrazinylmethyl)-1H-benzimidazol-2-yl]amino]-1-pyrrolidineacetonitrile (E)-2-butenedioate(1:1)
30 (compound 135);
3-[3-(2-pyridinylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-pyrrolidineacetonitrile; mp. 150 °C
(compound 136); and
4-[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]hexahydro-1H-azepine-1-acetonitrile; mp. 130 °C
(compound 137).

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Example 26

A mixture of 11 parts of 3-[1-(2-pyridinylmethyl)-1H-benzimidazol-2-yl]amino]-1-pyrrolidineacetonitrile and 320 parts of methanol, saturated with ammonia was hydrogenated at normal pressure and at room 40 temperature with 3 parts of Raney-nickel catalyst. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was solidified in 2,2'-oxybispropane while stirring. The product was filtered off and dried, yielding 10 parts (91%) of N[1-(2-aminoethyl)-3-pyrrolidinyl]-1-(2-pyridinylmethyl)-1H-benzimidazol-2-amine; mp. 130 °C (compound 138).

In a similar manner there were also prepared:

N-[1-(2-aminoethyl)-3-pyrrolidinyl]-1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-amine as a residue
45 (compound 139);
N[1-(2-aminoethyl)-3-pyrrolidinyl]-1-(2-pyrazinylmethyl)-1H-benzimidazol-2-amine as a residue (compound 140);
N[1-(2-aminoethyl)-3-pyrrolidinyl]-3-(2-pyridinylmethyl)-3H-imidazo[4,5-b]pyridin-2-amine as a residue
50 (compound 141); and
N[1-(2-aminoethyl)hexahydro-1H-azepin-4-yl]-1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-amine as a residue (compound 142).

Example 27

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A mixture of 16.8 parts of ethyl (2-chloroethyl)carbamate, 30 parts of N(3-pyrrolidinyl)-3-(2-thienylmethyl)-3H-imidazo[4,5-b]pyridin-2-amine, 21.2 parts of sodium carbonate and 270 parts of N, N-dimethylacetamide was stirred for 5 hours at 100 °C. After cooling, the reaction mixture was poured into ice

water and the product was extracted five times with 4-methyl-2-pentanone. The combined extracts were washed with water, dried, filtered and evaporated. The residue was converted into the (E)-2-butenedioate salt in 2-propanol and 1,1'-oxybisethane. The salt was filtered off and dried, yielding 30 parts (56.5%) of ethyl [2-[3-[[3-(2-thienylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-pyrrolidinyl]ethyl]carbamate (E)-2-butenedioate(1:1); mp. 187.8 °C (compound 143).

In a similar manner there were also prepared:

- ethyl [2-[3-[[1-(4-thiazolylmethyl)-1H-benzimidazol-2-yl]amino]-1-pyrrolidinyl]ethyl]carbamate as an oily residue (compound 144);
- ethyl [2-[3-[[5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-pyrrolidinyl]ethyl]carbamate (E)-2-butenedioate(1:2); mp. 165 °C (compound 145);
- ethyl [2-[3-[[3-(4-thiazolylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-pyrrolidinyl]ethyl]carbamate as a residue (compound 146); and
- ethyl [2-[hexahydro-4-[[1-[(5-methyl-2-furanyl)methyl]-1H-benzimidazol-2-yl]amino]-1H-azepin-1-yl]ethyl]carbamate as a residue (compound 147).

In a similar manner there is also prepared:

N-methyl-N'-[2-[hexahydro-4-[[1-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1H-azepin-1-yl]ethyl]urea (compound 148).

Example 28

To a stirred mixture of 85 parts of potassium hydroxide, 5 parts of water and 368 parts of 2-propanol were added 50.5 parts of ethyl [2-[hexahydro-4-[[1-[(5-methyl-2-furanyl)methyl]-1H-benzimidazol-2-yl]amino]-1H-azepin-1-yl]ethyl]carbamate (exothermic reaction, the mixture was cooled when the temperature reached 60 °C). The reaction mixture was refluxed for 2 hours. After cooling, the mixture was evaporated. The residue was taken up in 800 parts of water and the product was extracted three times with dichloromethane. The combined extracts were washed with a small amount of water, dried, filtered and evaporated. The residue was converted into the (E)-2-butenedioate salt in 320 parts of ethanol. The salt was filtered off, washed with ethanol and dried in vacuo at 40 °C, yielding 48.0 parts (55.8%) of N-[1-(2-aminoethyl)hexahydro-1H-azepin-4-yl]-1-[(5-methyl-2-furanyl)methyl]-1H-benzimidazol-2-amine (E)-2-butenedioate(1:3); mp. ≥145 °C (compound 149).

In a similar manner there were also prepared:

- N-[1-(2-aminoethyl)-3-pyrrolidinyl]-1-(4-thiazolylmethyl)-1H-benzimidazol-2-amine; decomposition >80 °C (compound 150);
- N-[1-(2-aminoethyl)-3-pyrrolidinyl]-3-(2-thienylmethyl)-3H-imidazo[4,5-b]pyridin-2-amine as a residue (compound 151);
- N-[1-(2-aminoethyl)-3-pyrrolidinyl]-1-(2-thienylmethyl)-1H-benzimidazol-2-amine (E)-2-butenedioate(1:3); mp. 150 °C (compound 152);
- [1-(2-aminoethyl)-3-pyrrolidinyl]-3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-amine as a residue (compound 153); and
- N-[1-(2-aminoethyl)-3-pyrrolidinyl]-3-(4-thiazolylmethyl)-3H-imidazo[4,5-b]pyridin-2-amine as a residue (compound 154).

Example 29

A mixture of 1.7 parts of 2-chloropyrimidine, 4.1 parts of N-[1-(2-aminoethyl)-3-pyrrolidinyl]-3-(4-thiazolylmethyl)-3H-imidazo[4,5-b]pyridin-2-amine, 2.1 parts of sodium carbonate and 108 parts of N,N-dimethylacetamide was stirred for 6 hours at 100 °C. After cooling, the reaction mixture was poured into 600 parts of water and the product was extracted with dichloromethane. The extract was washed with water, dried, filtered and evaporated. The residue was converted into the (E)-2-butenedioate salt in 2-propanone and ethanol. The salt was filtered off, washed with 2-propanone and crystallized from a mixture of 2,2'-oxybispropane and methanol (1:1 by volume). The product was filtered off, washed with 2-propanone and dried in vacuo at 60 °C, yielding 3.0 parts (32.1%) of N-[1-[2-(2-pyrimidinylamino)ethyl]-3-pyrrolidinyl]-3-(4-thiazolylmethyl)-3H-imidazo[4,5-b]pyridin-2-amine (E)-2-butenedioate(1:3), hemihydrate; mp. 161.7 °C (compound 155).

In a similar manner there were also prepared:

- N-[1-[2-(2-pyrimidinylamino)ethyl]-3-pyrrolidinyl]-1-(4-thiazolylmethyl)-1H-benzimidazol-2-amine (E)-2-butenedioate(2:3), monohydrate; mp. 89.4 °C (compound 156);
- 1-(2-pyrazinylmethyl)-N-[1-[2-(2-pyrimidinylamino)ethyl]-3-pyrrolidinyl]-1H-benzimidazol-2-amine (E)-2-

butenedioate(2:3), monohydrate; mp. 131.0 °C (compound 157);
 N-[1-[2-(2-pyrimidinylamino)ethyl]-3-pyrrolidinyl]-3-(2-pyridinylmethyl)-3H-imidazo[4,5-b]pyridin-2-amine (E)-2-butenedioate(1:3); mp. 119.7 °C (compound 158);
 N[1-[2-(2-pyrimidinylamino)ethyl]-3-pyrrolidinyl]-1-(2-thienylmethyl)-1H-benzimidazol-2-amine ethanedioate(1:3), hemihydrate; mp. 174.4 °C (compound 159);
 1-[(4-fluorophenyl)methyl]-N-[hexahydro-1-[2-(2-pyrimidinylamino)ethyl]-1H-azepin-4-yl]-1H-benzimidazol-2-amine ethanedioate(1:3); mp. 153.1 °C (compound 160); and
 1-[(5-methyl-2-furanyl)methyl]-N-[hexahydro-1-[2-(2-pyrimidinylamino)ethyl]-1H-azepin-4-yl]-1H-benzimidazol-2-amine ethanedioate(1:3); mp. 139.8 °C (compound 161).

10 In a similar manner there are also prepared:
 N-[hexahydro-1-[2-(2-pyrimidinylamino)ethyl]-1H-azepin-4-yl]-1-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]-pyridin-2-amine (compound 162);
 N-[hexahydro-2-(2-pyrazinylamino)ethyl]-1H-azepin-4-yl]-1-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]-pyridin-2-amine (compound 163);
 15 N-[hexahydro-1-[2-[(6-chloro-3-pyridazinyl)amino]ethyl]-1H-azepin-4-yl]-1-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-amine (compound 164);

Example 30

20 A mixture of 1.4 parts of 2-chloropyrimidine, 3.3 parts of N-[1-(2-aminoethyl)-3-pyrrolidinyl]-1-(2-pyridinylmethyl)-1H-benzimidazol-2-amine, 1.3 parts of sodium hydrogen carbonate and 60 parts of ethanol was stirred for 20 hours at reflux temperature. After filtration and evaporation of the filtrate, the residue was purified by column chromatography over silica gel using a mixture of trichloromethane, hexane, methanol and ammonium hydroxide (75:20:4.5:0.5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the (E)-2-butenedioate salt in 2-propanol. The salt was filtered off and crystallized from 2-propanol, yielding, after drying overnight at 80 °C, 2.3 parts (31.0%) of 1-(2-pyridinylmethyl)-N-[1-[2-(2-pyrimidinylamino)ethyl]-3-pyrrolidinyl]-1H-benzimidazol-2-amine (E)-2-butenedioate(2:3), 2-propanolate(2:1); mp. 134.8 °C (compound 165).

In a similar manner there were also prepared:

30 1-[(4-fluorophenyl)methyl]-N-[1-[2-(2-pyrimidinylamino)ethyl]-3-pyrrolidinyl]-1H-benzimidazol-2-amine; mp. 164.1 °C (compound 166); and
 N-[1-[2-(2-pyrimidinylamino)ethyl]-3-pyrrolidinyl]-3-(2-thienylmethyl)-3H-imidazo[4,5-b]pyridin-2-amine (E)-2-butenedioate(1:1); mp. 178.2 °C (compound 167).

Example 31

A mixture of 12.8 parts of 2-bromothiazole, 22 parts of N[1-(2-amino ethyl)-3-pyrrolidinyl]-1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-amine and 250 parts of pyridine was stirred and refluxed for 6 hours. After cooling, 12.8 parts of 2-bromothiazole were added and stirring was continued overnight at reflux temperature. The mixture was cooled and evaporated. The residue was taken up three times in methylbenzene and the latter was evaporated each time. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane, hexane, methanol and ammonium hydroxide (45:45:10:1 by volume) as eluent. The pure and the less pure fractions were collected and the eluent was evaporated. The residue was purified by column chromatography (HPLC) over silica gel using a mixture of trichloromethane, 45 methanol and methanol, saturated with ammonia, (96:3:1 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from a mixture of 2,2'-oxybispropane and 2-propanone. The product was filtered off and dried, yielding 2.0 parts (7.3%) of 1-[(4-fluorophenyl)methyl]-N[1-[2-(2-thiazolylamino)ethyl]-3-pyrrolidinyl]-1H-benzimidazol-2-amine; mp. 127.1 °C (compound 168).

Example 32

To a stirred mixture of 1 part of a sodium hydride dispersion 50% and 94 parts of N,N-dimethylformamide is added dropwise a solution of 5.5 parts of hexahydro-4-[[3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1H-azepine-1-ethanol in N,N-dimethylformamide. Upon complete addition, stirring is continued for 15 minutes at room temperature. 1.9 Parts of 2-chloropyrimidine are added portionwise and upon completion, stirring is continued for 2 hours at room temperature. The reaction mixture is decomposed with water and the product is extracted with dichloromethane.

The extract is dried, filtered and evaporated. The residue is purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions are collected and the eluent was evaporated. The residue is converted into the ethanedioate salt in ethanol. The salt is filtered off and dried, yielding 3.4 parts (34.8%) of N-[hexahydro-1-[2-(2-pyrimidinyloxy)ethyl]-1H-azepin-4-yl]-3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-amine (compound 169).

In a similar manner there is also prepared:

N-[hexahydro-1-[2-thiazolyloxy)ethyl]-1H-azepin-4-yl]-3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-amine (compound 170).

10 Example 33

To a stirred mixture of 4.2 parts of N,N-methyltetraethylbis[cyclohexanamine] and 90 parts of tetrahydrofuran were added 10.6 parts of carbon disulfide. After stirring for 10 minutes, a solution of 6 parts of N[1-(2-aminoethyl)-3-pyrrolidinyl]-3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-amine in 36 parts of tetrahydrofuran was added dropwise to the thus obtained mixture (exothermic reaction, the temperature rose to 26 °C). Upon complete addition, stirring was continued for 30 minutes at room temperature. The reaction mixture was evaporated and the residue was taken up in 240 parts of acetonitrile. The precipitate was filtered off and the filtrate was evaporated, yielding 6.9 parts (100%) of N-[1-(2-isothiocyanatoethyl)-3-pyrrolidinyl]-3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-amine as a residue (compound 171).

In a similar manner there were also prepared:

1-[(4-fluorophenyl)methyl]-N-[1-(2-isothiocyanatoethyl)-3-pyrrolidinyl]-1H-benzimidazol-2-amine as an oily residue (compound 172);
N-[1-(2-isothiocyanatoethyl)-3-pyrrolidinyl]-1-(4-thiazolylmethyl)-1H-benzimidazol-2-amine as a residue (compound 173);
N[1-(2-isothiocyanatoethyl)-3-pyrrolidinyl]-3-(2-thienylmethyl)-3H-imidazo[4,5-b]pyridin-2-amine as a residue (compound 174);
N[1-(2-isothiocyanatoethyl)-3-pyrrolidinyl]-1-(2-thienylmethyl)-1H-benzimidazol-2-amine as an oily residue (compound 175); and
N-[1-(2-isothiocyanatoethyl)-3-pyrrolidinyl]-3-(4-thiazolylmethyl)-3H-imidazo[4,5-b]pyridin-2-amine as a residue (compound 176).

Example 34

A mixture of 2.8 parts of 3,4-pyridinediamine, 10.7 parts of 1-[(4-fluorophenyl)methyl]-N-[1-(2-isothiocyanatoethyl)-3-pyrrolidinyl]-1H-benzimidazol-2-amine and 90 parts of tetrahydrofuran was stirred and refluxed for 7 hours. The precipitated product was filtered off while hot, washed with a small amount of tetrahydrofuran and dried, yielding 6.5 parts (51%) of N-(4-amino-3-pyridinyl)-N'-[2-[3-[[1-(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-pyrrolidinyl]ethylthiourea; mp. 225 °C (compound 177).

In a similar manner there were also prepared:

N-(4-amino-3-pyridinyl)-N'-[2-[3-[[1-(4-thiazolylmethyl)-1H-benzimidazol-2-yl]amino]-1-pyrrolidinyl]ethyl]thiourea; mp. 220.0 °C (compound 178);
N-(4-amino-3-pyridinyl)-N'-[2-[3-[[3-(2-thienylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-pyrrolidinyl]ethyl]thiourea; mp. 172.2 °C (compound 179);
N(4-amino-3-pyridinyl)-N'-[2-[3-[[1-(2-thienylmethyl)-1H-benzimidazol-2-yl]amino]-1-pyrrolidinyl]ethyl]thiourea as a residue (compound 180);
N(4-amino-3-pyridinyl)-N'-[2-[3-[[3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-pyrrolidinyl]ethyl]thiourea as a residue (compound 181); and
N(4-amino-3-pyridinyl)-N'-[2-[3-[[3-(4-thiazolylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-pyrrolidinyl]ethyl]thiourea as a residue (compound 182).

Example 35

A mixture of 10.5 parts of N-(4-amino-3-pyridinyl)-N'-[2-[3-[[3-(4-thiazolylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-pyrrolidinyl]ethyl]thiourea, 11.5 parts of mercury(II) oxide, 0.1 parts of sulfur and 168 parts of methanol, saturated with ammonia was stirred for 30 minutes at reflux temperature. The reaction mixture was filtered while hot over diatomaceous earth and washed with warm methanol. The filtrate was evaporated and the residue was purified by column chromatography over silica gel using a mixture of

trichloromethane, methanol and ammonium hydroxide (90:9:1 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the (E)-2-butenedioate salt in 160 parts of 2-propanone and 160 parts of ethanol. The salt was filtered off and dried, yielding 4.1 parts (23.1%) of N-[1-[2-[(1H-imidazo[4,5-c]pyridin-2-yl)amino]ethyl]-3-pyrrolidinyl]-3-(4-thiazolylmethyl)-3H-imidazo[4,5-b]pyridin-2-amine (E)-2-butenedioate(1:3), dihydrate; mp. 157.2°C (compound 183).

In a similar manner there were also prepared:

N-[2-[3-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-pyrrolidinyl]ethyl]-1H-imidazo[4,5-c]pyridin-2-amine monohydrate; mp. 140.1°C (compound 184);
 10 N-[2-[3-[[1-(4-thiazolylmethyl)-1H-benzimidazol-2-yl]amino]-1-pyrrolidinyl]ethyl]-1H-imidazo[4,5-c]pyridin-2-amine ethanedioate(1:4); mp. 173.6°C (compound 185);
N-[2-[3-[[1-2-thienylmethyl]-1H-benzimidazol-2-yl]amino]-1-pyrrolidinyl]ethyl]-1H-imidazo[4,5-c]pyridin-2-amine ethanedioate(1:4); mp. 180.9°C (dec.) (compound 186); and
N-[1-[2-[(1H-imidazo[4,5-c]pyridin-2-yl)amino]ethyl]-3-pyrrolidinyl]-3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-amine ethanedioate(2:5), dihydrate; mp. 88.7°C (compound 187).

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Example 36

A mixture of 0.9 parts of isocyanatomethane, 5.3 parts of N-[1-(2-aminoethyl)-3-pyrrolidinyl]-1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-amine and 63 parts of tetrahydrofuran was stirred for 1.5 hour at room temperature using a CaCl_2 -tube. Another portion of 0.9 parts of isocyanatomethane was added and stirring was continued for 1.5 hour at room temperature. The precipitated product was filtered off, washed with tetrahydrofuran and dried in vacuo at room temperature, yielding 5.0 parts (81%) of N-[2-[3-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-pyrrolidinyl]ethyl]-N'-methylurea; mp. 161.1°C (compound 188).

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In a similar manner there was also prepared:

N-[2-[3-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-pyrrolidinyl]ethyl]-N'-methylthiourea; mp. 169.0°C (compound 189).

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Example 37

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To a stirred mixture of 1.12 parts of 3-furancarboxylic acid, 2.02 parts of N,N-diethylethanamine and 195 parts of dichloromethane are added 2.6 parts of 2-chloro-1-methylpyridinium iodide at room temperature. After stirring for 1 hour, 3.3 parts of N-[1-(2-aminoethyl)-hexahydro-1H-azepin-4-yl]-3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-amine are added and stirred overnight at room temperature. The mixture is poured into water and the layers are separated. The organic layer is dried, filtered and evaporated. The residue is purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (96:4 by volume) as eluent. The pure fractions are collected and the eluent is evaporated, yielding 2.19 parts (36.1%) of N-[2-(hexahydro-4-[[3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1H-azepin-4-yl]ethyl]-3-furancarboxamide as a residue (compound 190).

40

In a similar manner there are also prepared:

N-[2-hexahydro-4-[[3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1H-azepin-4-yl]-ethyl]-2-thiazolecarboxamide (compound 191); and
 2-amino-N-[2-hexahydro-4-[[3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1H-azepin-4-yl]ethyl]benzamide (compound 192).

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Example 38

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A mixture of 6 parts of 3-[(5-methyl-2-furanyl)methyl]-N-(3-pyrrolidinyl)-3H-imidazo[4,5-b]pyridin-2-amine monohydrochloride, 2 parts of poly(oxymethylene), 1 part of a solution of thiophene in methanol 4%, 160 parts of methanol and 6 parts of potassium acetate was hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was taken up in water and a small amount of concentrated ammonium hydroxide was added. The product was extracted twice with trichloromethane. The combined extracts were washed with water, dried, filtered and evaporated. The oily residue was converted into the (E)-2-butenedioate salt in 320 parts of 2-propanone. The salt was filtered off, washed with 2-propanone and crystallized from 2-propanol. The product was filtered off and dried in vacuo at 60°C, yielding 1.5 parts (15.3%) of 3-[(5-methyl-2-furanyl)methyl]-N-(1-methyl-3-pyrrolidinyl)-3H-imidazo[4,5-b]pyridin-2-amine (E)-2-butenedioate(1:2); mp. 168.6°C (compound 193).

In a similar manner there were also prepared:

N-(1-methyl-3-pyrrolidinyl)-3-(2-pyridinylmethyl)-3H-imidazo[4,5-b]pyridin-2-amine ethanedioate(1:2); mp. 163.6 °C (compound 194); and
 N-(1-methyl-3-pyrrolidinyl)-3-(4-thiazolylmethyl)-3H-imidazo[4,5-b]pyridin-2-amine ethanedioate(1:2); mp. 196.3 °C (compound 195).

Example 39

A mixture of 3.1 parts of 3-(2-furanyl methyl)-N-(hexahydro-1H-azepin-4-yl)-3H-imidazo[4,5-b]pyridin-2-amine, 2 parts of poly(oxymethylene), 1 part of a solution of thiophene in methanol 4% and 120 parts of methanol was hydrogenated at normal pressure and at 50 °C with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol, saturated with ammonia, (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the ethanedioate salt in 2-propanol. The salt was filtered off and crystallized from methanol. The product was filtered off and dried, yielding 2.2 parts (43.5%) of 3-(2-furanyl methyl)-N-(hexahydro-1-methyl-1H-azepin-4-yl)-3H-imidazo[4,5-b]pyridin-2-amine ethanedioate(1:2); mp. 183.5 °C (compound 196).

In a similar manner there were also prepared:

1-[(4-fluorophenyl)methyl]-N-(hexahydro-1-methyl-1H-azepin-4-yl)-1H-benzimidazol-2-amine (E)-2-butenedioate(1:2); mp. 209.2 °C (compound 197);
 N-(hexahydro-1-methyl-1H-azepin-4-yl)-1-[(5-methyl-2-furanyl)methyl]-1H-benzimidazol-2-amine ethanedioate(1:2); mp. 207.6 °C (compound 198);
 9-[(4-fluorophenyl)methyl]-N-(hexahydro-1-methyl-1H-azepin-4-yl)-9H-purin-8-amine; mp. 117.2 °C (compound 199);
 1-[(4-fluorophenyl)methyl]-N-(hexahydro-1-methyl-1H-azepin-4-yl)-1H-imidazo[4,5-c]pyridin-2-amine; mp. 170.1 °C (compound 200);
 N-[hexahydro-1-(1-methylethyl)-1H-azepin-4-yl]-3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-amine (E)-2-butenedioate(1:2); mp. 110.1 °C (compound 201);
 N-(hexahydro-methyl-1H-azepin-4-yl)-3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-c]pyridin-2-amine; mp. 107.7 °C (compound 202);
 1-[(4-fluorophenyl)methyl]-N-(1-methyl-3-pyrrolidinyl)-1H-benzimidazol-2-amine; mp. 138.7 °C (compound 203);
 1-[(4-fluorophenyl)methyl]-N-[1-(1-methylethyl)-3-pyrrolidinyl]-1H-benzimidazol-2-amine; mp. 135.5 °C (compound 204); and
 N-(1-methyl-3-pyrrolidinyl)-1-(2-thienylmethyl)-1H-benzimidazol-2-amine ethanedioate(1:2); mp. 225.2 °C (compound 205).

Example 40

A mixture of 6 parts of N-(hexahydro-1H-azepin-4-yl)-3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5,b]pyridin-2-amine ethanedioate(1:2) and 64 parts of methanol, saturated with ammonia was stirred for 5 minutes at reflux temperature. After cooling, the precipitate was filtered off and the filtrate was evaporated. A mixture of the residue, 5 parts of cyclohexanone, 1 part of a solution of thiophene in methanol 4% and 120 parts of methanol was hydrogenated at normal pressure and at room temperature with 1 part of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was converted into the ethanedioate salt in a small amount of 2-propanone and ethanol. After cooling, the salt was filtered off and crystallized from ethanol. The product was filtered off and dried, yielding 2 parts (23.9%) of N-(1-cyclohexylhexahydro-1H-azepin-4-yl)-3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-amine ethanedioate(1:2), hemihydrate; mp. 136.1 °C (compound 206).

In a similar manner there was also prepared:

N-(hexahydro-1-methyl-1H-azepin-4-yl)-3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-amine ethanedioate(1:2); mp. 174.2 °C (compound 207).

55

Example 41

A mixture of 1.3 parts of 2-ethenylpyridine, 6.2 parts of 1-[(4-fluorophenyl)methyl]-N-(3-pyrrolidinyl)-1H-

benzimidazol-2-amine and 56 parts of 1-butanol was stirred and refluxed for 3 hours. Another 3.5 parts of 2-ethenylpyridine were added and stirring at reflux was continued for 3.5 hours. The reaction mixture was evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (90:9:1 by volume) as eluent. The pure fractions were collected and the 5 eluent was evaporated. The residue was converted into the ethanedioate salt in 2-propanone. The salt was filtered off and dried in vacuo at 60 °C, yielding 8.0 parts (54%) of 1-[(4-fluorophenyl)methyl]-N-[1-(2-pyridinyl)ethyl]-3-pyrrolidinyl]-1H-benzimidazol-2-amine ethanedioate(2:7); mp. 194.0 °C (compound 208).

Example 42

10 Gazeous oxirane was bubbled through a stirred mixture of 6.2 parts of 1-[(4-fluorophenyl)methyl]-N-(3-pyrrolidinyl)-1H-benzimidazol-2-amine and 120 parts of methanol for 1.50 hour at 30 °C. The reaction mixture was evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane, methanol and ammonium hydroxide (90:9:1 by volume) as eluent. The pure 15 fractions were collected and the eluent was evaporated. The residue was converted into the hydrochloride salt in 2-propanol. The salt was filtered off, washed with 2-propanone and dried in vacuo at 80 °C, yielding 3.8 parts (44%) of 3-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]amino]-1-pyrrolidineethanol dihydrochloride; mp. 230.3 °C (compound 209).

In a similar manner there is also prepared:

20 hexahydro-4-[[3-[(5-methyl-2-furanyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl]amino]- α -(phenoxyethyl)-1H-azepine-1-ethanol (compound 210).

Example 43

25 A mixture of 11.3 parts of N-(hexahydro-1H-azepin-4-yl)-1-[(5-methyl-2-furanyl)methyl]-1H-benzimidazol-2-amine (E)-2-butenedioate(2:3), hemihydrate, 10.6 parts of sodium carbonate and 120 parts of methanol was stirred for 30 minutes at reflux temperature. After cooling to 30 °C, gaseous oxirane was bubbled during 2 hours through the mixture. The reaction mixture was evaporated and the residue was stirred in dichloromethane. The precipitate was filtered off over diatomaceous earth and the filtrate was evaporated. 30 The residue was purified by column chromatography over silica gel using a mixture of trichloromethane, methanol and ammonium hydroxide (90:9:1 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the ethanedioate salt in 2-propanone. The salt was filtered off and crystallized from a mixture of 2-propanone and ethanol. The product was filtered off and dried, yielding 0.7 parts (6.3%) of hexahydro-4-[[1-[(5-methyl-2-furanyl)methyl]-1H-benzimidazol-2-yl]-35 amino]-1H-azepine-1-ethanol ethanedioate(1:2); mp. 155.8 °C (compound 211).

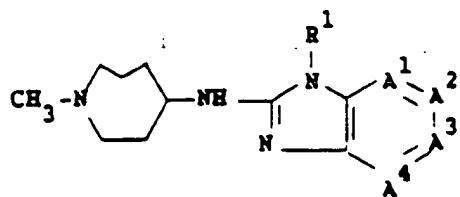
Example 44

40 5 Parts of N-(3-pyrrolidinyl)-1-(2-thienylmethyl)-1H-benzimidazol-2-amine were converted into the ethanedioate salt in a mixture of methanol and 2-propanone. The salt was filtered off, washed with 2-propanone and the product was boiled in 160 parts of ethanol. The mixture was allowed to cool while stirring. The precipitated product was filtered off and dried, yielding 2.8 parts (42.4%) of N-(3-pyrrolidinyl)-1-(2-thienylmethyl)-1H-benzimidazol-2-amine ethanedioate(1:1); mp. 222.5 °C (compound 212).

45 Example 45

To a stirred and heated (50 °C) mixture of 6.4 parts of lithium tetrahydroaluminate and 450 parts of tetrahydrofuran were added portionwise 23.5 parts of ethyl 4-(1H-benzimidazol-2-ylamino)hexahydro-1H-azepine-1-carboxylate under nitrogen atmosphere. Upon complete addition, stirring was continued for 2 hours at reflux temperature. The reaction mixture was decomposed with ethyl acetate, 30 parts of a sodium hydroxide solution and 30 parts of water. The whole was filtered over diatomaceous earth and the filtrate was evaporated. The residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 10.5 parts (55.0%) of N-(hexahydro-1-methyl-1H-azepin-4-yl)-1H-benzimidazol-2-amine; mp. 168.3 °C (compound 213).

55 In a similar manner ther were also prepar d:



10

Comp. No.	R ¹	A ¹ -A ² -A ³ -A ⁴	base/ salt	mp (°C)
15 214	4-F-C ₆ H ₄ -CH ₂ -	CH=CH-C(OCH ₃)=CH	(E)-2-butene-dioate (1:2)	181.6
215	4-F-C ₆ H ₄ -CH ₂ -	CH=C(OCH ₃)-CH=CH	base	165.6
20 216	C ₆ H ₅ -CH ₂ -	CH=CH-CH=CH	base	100.4
217	4-CH ₃ -C ₆ H ₄ -CH ₂ -	CH=CH-CH=CH	(E)-2-butene-dioate (1:2)	225.5
218	4-F-C ₆ H ₄ -CH ₂ -	CH=CH-CH=CH	(E)-2-butene-dioate (1:2)	208.8
25 219	4-F-C ₆ H ₄ -CH ₂ -	CH=CH-C(CH ₃)=CH	(E)-2-butene-dioate (1:2)	214.5
220	C ₂ H ₅ -	CH=CH-CH=CH	2 HCl 1/2 H ₂ O	219.4
30 221	2-thienylmethyl	CH=CH-CH=CH	(E)-2-butene-dioate (2:3)	158.6
222	4-F-C ₆ H ₄ -CH ₂ -	CH=C(F)-C(F)=CH	(E)-2-butene-dioate (1:2)	194.9
35 223	(4-F-C ₆ H ₄) ₂ CH-	CH=CH-CH=CH	2 (COOH) ₂	170.3
224	2-pyridinylmethyl	CH=CH-CH=CH		
225	2-pyrazinylmethyl	CH=CH-CH=CH		
40 226	4-thiazolylmethyl	CH=CH-CH=CH		
227	(5-methyl-1H-imidazol-4-yl)methyl	CH=CH-CH=CH		
45 228	(5-methyl-2-furanyl)methyl	CH=CH-CH=CH		

C) Pharmacological Examples

50

The useful anti-histaminic properties of the compounds of formula (i) which can be used as the active ingredient in the formulations according to the present invention can be demonstrated by the following test procedure.

55 Example 46

Protection of rats from compound 48/80-induced lethality.

Compound 48/80, a mixture of oligomers obtained by condensation of 4-methoxy-N-methylbenzeneethanamine and formaldehyde has been described as a potent histamine releasing agent (Int. Arch. Allergy, 13, 336 (1958)). The protection from compound 48/80-induced lethal circulatory collapse appears to be simple way of evaluating quantitatively the antihistaminic activity of test compounds. Male rats of an inbred Wistar strain, weighing 240-260 g were used in the experiment. After overnight starvation the rats were transferred to conditioned laboratories (temp. = 21 ± 1 °C, relative humidity = 65 ± 5%). The rats were treated subcutaneously or orally with a test compound or with the solvent (NaCl solution, 0.9%). One hour after treatment there was injected intravenously compound 48/80, freshly dissolved in water, at a dose of 0.5 mg/kg (0.2 ml/100 g of body weight). In control experiments, wherein 250 solvent-treated animals were injected with the standard dose of compound 48/80, not more than 2.8% of the animals survived after 4 hours. Survival after 4 hours is therefore considered to be a safe criterion of a protective effect of drug administration. The ED₅₀-values of the compounds of formula (I) are listed in table 1. Said ED₅₀-values are the values in mg/kg body weight at which the tested compounds protect 50% of the tested animals against compound 48/8-induced lethality.

15

Table 1

No.	compound 48/80 lethality test in rats-ED ₅₀ in mg/kg body weight
20 49	0.04
61	0.08
68	0.04
94	0.04
25 95	0.04
96	0.04
99	0.04
102	0.04
109	0.04
30 125	0.08
166	0.08
168	0.08
186	0.01
187	0.04
35 188	0.01
207	0.01
196	0.02
198	0.04
204	0.04
40 211	0.04

D) Composition Examples

45 The following formulations exemplify typical pharmaceutical compositions in dosage unit from suitable for systemic administration to animal and human subjects in accordance with the instant invention.

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof.

50 Example 47 : ORAL DROPS

55 500 g of the A.I. was dissolved in 0.5 l of 2-hydroxypropanoic acid and 1.5 l of the polyethylene glycol at 60-80 °C. After cooling to 30-40 °C there were added 35 l of polyethylene glycol and the mixture was stirred well. Then there was added a solution of 1750 g of sodium saccharin in 2.5 l of purified water and while stirring there were added 2.5 l of cocoa flavor and polyethylene glycol q.s. to a volume of 50 l, providing an oral drop solution comprising 10 mg of the A.I. per ml. The resulting solution was filled into suitable containers.

Example 48: ORAL SOLUTION

9 g of methyl 4-hydroxybenzoate and 1 g of propyl 4-hydroxybenzoate were dissolved in 4 l of boiling purified water. In 3 l of this solution were dissolved first 10 g of 2,3-dihydroxybutanedioic acid and thereafter 5 20 g of the A.I. The latter solution was combined with the remaining part of the former solution and 12 l 1,2,3-propanetriol and 3 l of sorbitol 70% solution were added thereto. 40 g of sodium saccharin were dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence were added. The latter solution was combined with the former, water was added q.s. to a volume of 20 l providing an oral solution comprising 20 mg of the active ingredient per teaspoonful (5 ml). The resulting solution was filled in suitable 10 containers.

Example 49 : CAPSULES

20 g of the A.I., 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 15 1.2 g magnesium stearate were vigorously stirred together. The resulting mixture was subsequently filled into 1000 suitable hardened gelating capsules, comprising each 20 mg of the active ingredient.

Example 50 : FILM-COATED TABLETS20 Preparation of tablet core

A mixture of 100 g of the A.I., 570 g lactose and 200 g starch was mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinylpyrrolidone (Kollidon-K 90®) in about 200 25 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added 100 g microcrystalline cellulose (Avicel®) and 15 g hydrogenated vegetable oil (Sterotex ®). The whole was mixed well and compressed into tablets, giving 10.000 tablets, each containing 10 mg of the active ingredient.

Coating

30 To a solution of 10 g methyl cellulose (Methocel 60 HG®) in 75 ml of denatured ethanol there was added a solution of 5 g of ethyl cellulose (Ethocel 22 cps ®) in 150 ml of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 g of polyethylene glycol was molten and dissolved in 75 ml of dichloromethane. The latter solution was added to the former and then there were added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated colour 35 suspension (Opaspray K-1-2109®) and the whole of homogenized.

The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Example 51: INJECTABLE SOLUTION

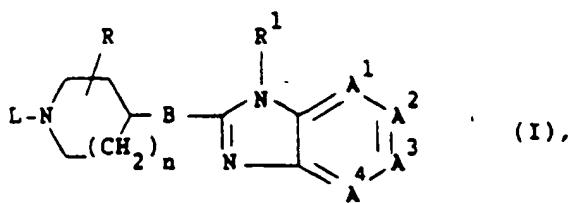
40 1.8 g methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50 °C there were added while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I..
The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 l volume, giving a solution of 4 mg A.I. per ml. The solution was sterilized by filtration (U.S.P. XVII p. 811) and filled in 45 sterile containers.

Example 52 : SUPPOSITORIES

50 3 g A.I. was dissolved in a solution of 3 g 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 g Surfactant (SPAN®) and triglycerides (Witepsol 555 ®) q.s. ad 300 g were molten together. The latter mixture was mixed well with the former solution. The thus obtained mixture was poured into moulds at a temperature of 37-38 °C to form 100 suppositories each containing 30 mg of the active ingredient.

Claims

55 1. A chemical compound having the formula



10 a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof, wherein
-A¹ = A²-A³ = A⁴⁻ is a bivalent radical having the formula

- CH = CH-CH = CH- (a-1),
- N = CH-CH = CH- (a-2),
- CH = N-CH = CH- (a-3),
- CH = CH-N = CH- (a-4),
- CH = CH-CH = N- (a-5),
- N = CH-N = CH- (a-6), or
- CH = N-CH = N- (a-7),

20 wherein one or two hydrogen atoms in said radicals (a-1) - (a-7) may, each independently from each other, be replaced by halo, C₁-₆alkyl, C₁-₆alkyloxy, trifluoromethyl or hydroxy;

R¹ is hydrogen, C₁-₁₀alkyl, C₃-₆cycloalkyl, Ar¹ or C₁-₆alkyl substituted with one or two Ar¹ radicals;

25 B is NR², CH₂, O, S, SO or SO₂; said R² being hydrogen, C₁-₆alkyl, C₃-₆cycloalkyl, C₁-₆alkylcarbonyl, C₁-₆alkyloxycarbonyl and Ar²-C₁-₆alkyl;

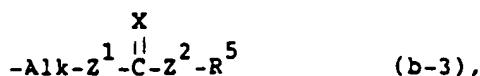
R is hydrogen or C₁-₆alkyl;

n is 0 or 2;

30 L is hydrogen, C₁-₆alkylcarbonyl, C₁-₆alkylsulfonyl, C₁-₆alkyloxycarbonyl, Ar²-C₁-₆alkyloxycarbonyl, Ar²-carbonyl, Ar²-sulfonyl, C₃-₆cycloalkyl, C₂-₆alkenyl optionally substituted with Ar², C₁-₁₂alkyl, a radical of formula

- Alk-R³ (b-1)
- Alk-Y-R⁴ (b-2)

35



40

or

-CH₂-CHOH-CH₂-O-R⁶ (b-4); wherein

R³ is Ar², Het, cyano, isocyanato, isothiocyanato, Ar²-sulfonyl or halo;

45 R⁴ is hydrogen, Ar², Het or C₁-₆alkyl optionally substituted with halo, Ar² or Het;

R⁵ is hydrogen, Ar², Het or C₁-₆alkyl optionally substituted with halo, Ar² or Het;

R⁶ is Ar² or naphthalenyl;

Y is O, S, NR⁷;

said R⁷ being hydrogen, C₁-₆alkyl, C₁-₆alkylcarbonyl or Ar¹-carbonyl;

50 Z¹ and Z² each independently are O, S, NR⁸ or a direct bond;

said R⁸ being hydrogen or C₁-₆alkyl;

X is O, S or NR⁹;

said R⁹ is hydrogen, C₁-₆alkyl or cyano;

each Alk independently being C₁-₆alkanediyl;

55 Het is a five- or six-membered heterocyclic ring containing 1, 2, 3 or 4 heteroatoms, said heteroatoms being selected from the group consisting of oxygen, sulfur and nitrogen, provided that no more than two oxygens or sulfurs are present, said five or six-membered ring being optionally condensed with a five- or six-membered carbocyclic or heterocyclic ring also containing 1, 2, 3 or 4

heteroatoms, the latter heteroatoms being selected from the group consisting of oxygen, sulfur and nitrogen, provided that no more than 2 oxygens or sulfurs are present, and when said Het is a bicyclic ring system it may optionally be substituted with up to 6 substituents, and when said Het is a monocyclic ring system it may optionally be substituted with up to 3 substituents, said substituents of Het being selected from the group consisting of a bivalent radical of formula =X; halo; isocyanato; isothiocyanato; nitro; cyano; trifluoromethyl; a radical of formula -A; a radical of formula -Y-A; or a radical of formula -Z¹-C(=X)-Z²-A; wherein said =X independently has the same meaning of the previously defined X and A is hydrogen, Ar² or C₁₋₆alkyl being optionally substituted with Ar², C₁₋₆alkyloxy, Ar²-O, hydroxy, or C₁₋₆alkyloxycarbonyl; and Y, Z¹ and Z² independently have the same meaning of the previously defined Y, Z¹ and Z²; provided that when in the radical -Z¹-C(=X)-Z²-A, A is hydrogen and Z¹ is NR⁸, O or S, then Z² is other than O or S;

Ar¹ is a member selected from the group consisting of phenyl, being optionally substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, mercapto, amino, mono- and di(C₁₋₆alkyl)amino, carboxyl, C₁₋₆alkyloxycarbonyl and C₁₋₆alkylcarbonyl; thieryl; halothienyl; furanyl; C₁₋₆alkyl substituted furanyl; pyridinyl; pyrimidinyl; pyrazinyl; thiazolyl and imidazolyl optionally substituted with C₁₋₆alkyl; and

Ar² is a member selected from the group consisting of phenyl being optionally substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, mercapto, amino, mono- and di(C₁₋₆alkyl)-amino, carboxyl, C₁₋₆alkyloxycarbonyl and C₁₋₆alkylcarbonyl.

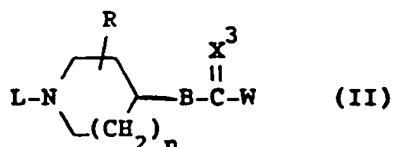
2. A chemical compound according to claim 1 wherein n = 2.
- 25 3. A chemical compound according to claim 1 wherein n = 0.
4. A chemical compound according to claim 1 wherein
Het is (i) an optionally substituted five- or six-membered heterocyclic ring containing 1, 2, 3 or 4 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, provided that no more than two oxygens or sulfurs are present; or
Het is (ii) an optionally substituted five- or six-membered heterocyclic ring containing 1 or 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, being ortho-condensed with an optionally substituted five- or six-membered ring through two ring carbon atoms or one ring carbon and one ring nitrogen atom, containing in the remainder of the condensed ring only carbon atoms; or
Het is (iii) an optionally substituted five- or six-membered heterocyclic ring containing 1 or 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, being ortho-condensed with an optionally substituted five- or six-membered heterocyclic ring through two ring carbon atoms or one ring carbon and one ring nitrogen atom, containing in the remainder of the condensed ring 1 or 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen; wherein Het may optionally be substituted with up to 2 substituents when Het is a monocyclic ring system, and wherein Het may optionally be substituted with up to 5 substituents when Het is a bicyclic ring system, said substituents of Het being selected from the group consisting of a bivalent radical of formula =X; halo; isocyanato; isothiocyanato; nitro; cyano; trifluoromethyl; a radical of formula -A; a radical of formula -Y-A; or a radical of formula -Z¹-C(=X)-Z²-A; wherein said =X independently has the same meaning of the previously defined X and A is hydrogen, Ar² or C₁₋₆alkyl being optionally substituted with Ar², C₁₋₆alkyloxy, Ar²-O, hydroxy, or C₁₋₆alkyloxycarbonyl; and Y, Z¹ and Z² independently have the same meaning of the previously defined Y, Z¹ and Z²; provided that when in the radical -Z¹-C(=X)-Z²-A, A is hydrogen and Z¹ is NR⁸, O or S, then Z² is other than O or S.
- 50 5. A chemical compound according to claim 4 wherein R is hydrogen, R¹ is C₁₋₆alkyl substituted with one Arⁱ and B is NR¹ or CR²H₂.
6. A chemical compound according to claim 5 wherein L is hydrogen, C₁₋₆alkyl or a radical of formula (b-1), (b-2) or (b-3) and B is NH.
- 55 7. A chemical compound according to claim 6 wherein R³, R⁴ and R⁵ are each Ar² or Het, R⁷ is hydrogen or C₁₋₆alkyl, X is O, and Z¹ and Z² are each independently NH or a direct bond.

8. A pharmaceutical composition comprising a suitable pharmaceutical carrier and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 7.

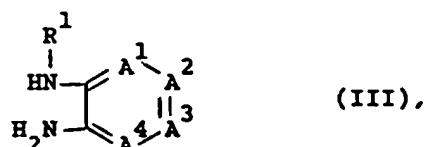
9. A method of preparing a pharmaceutical composition, characterized in that a therapeutically effective amount of a compound as defined in any of claims 1 to 7 is intimately mixed with suitable pharmaceutical carriers.

10. A compound as claimed in any one of claims 1 to 7 for use as a medicine.

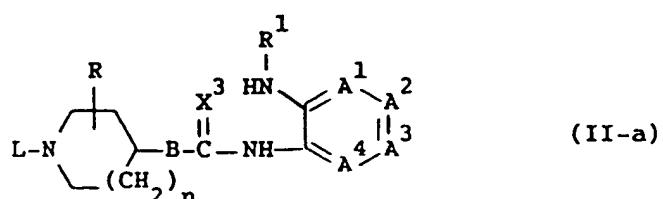
10 11. A process for preparing a chemical compound as claimed in any one of claims 1 to 7, characterized by
a) reacting a pyrrolidine or hexahydro-1H-azepine of formula



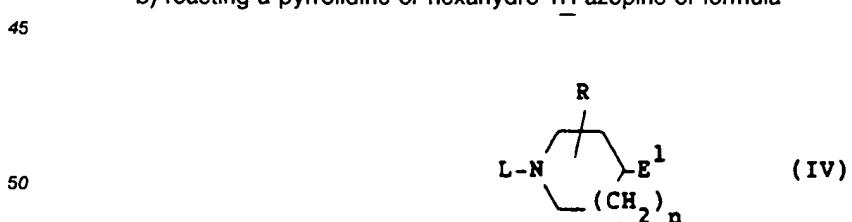
20 wherein X³ is O, S or NH and W is a reactive leaving group, with an aromatic diamine of formula



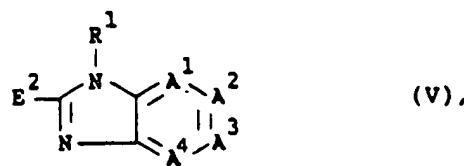
30 in a reaction-inert medium, said reaction proceeding in some instances via an intermediate of formula



40 which may in situ, or if desired, after isolating and further purifying it, be cyclized to yield the desired compounds of formula (I);
b) reacting a pyrrolidine or hexahydro-1H-azepine of formula



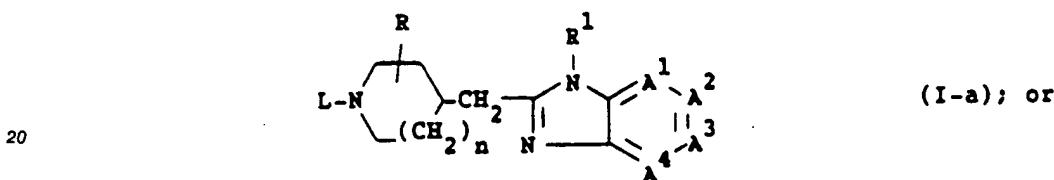
55 with an intermediate of formula



in a reaction-inert solvent if desired in the presence of a reductant, wherein:

10 i) E¹ is a radical of formula -B-M wherein M is hydrogen or an alkali metal or earth alkaline metal and E² is a radical of formula -W; or
 ii) E¹ is a radical of formula -W¹ and E² is a radical of formula M-B-; or
 iii) E¹ is a radical of formula -CH₂W¹ and E² is a radical of formula -M, thus preparing a compound of formula

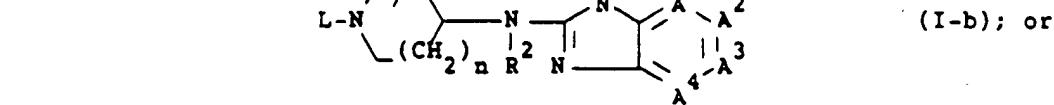
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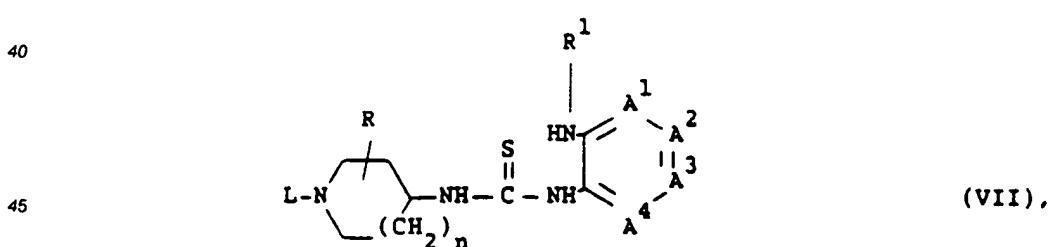
iv) E¹ is a radical of formula -M and E² is a radical of formula -CH₂-W¹, thus preparing a compound of formula (I-a); or
 v) E¹ is a radical of formula =O and E² is a radical of formula R²-NH-, thus preparing a compound of formula

30

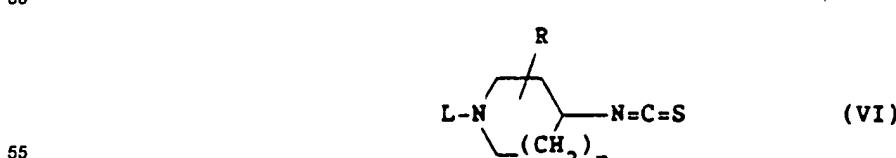


c) cyclodesulfurizing an intermediate of formula

40



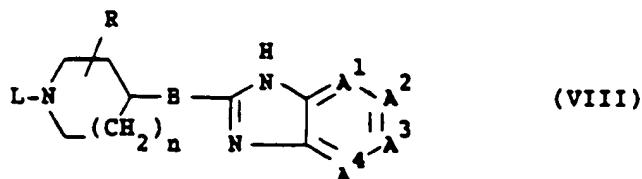
50



with a diamine of formula (III).

with an alkylhalide, metal oxide or metal salt in a reaction-inert solvent;
 d) N-alkylating an intermediate of formula

5



10

with a reagent of formula

15



wherein W^1 is a reactive leaving group, in a reaction-inert medium; or

e) N-alkylating a compound of formula H-D (I-d) with a reagent of formula L^1-W^1 (X) in a reaction-inert solvent, thus preparing a compound of formula L^1-D (I-c), wherein L^1 has the previously defined meaning of L, provided that it is other than hydrogen;

f) reductively N-alkylating a compound of formula H-D (I-d) with a ketone or aldehyde of formula $L^2=O$ (XI), said $L^2=O$ being an intermediate of formula L^2H_2 wherein two geminal hydrogen atoms are replaced by =O, in a reaction inert medium thus preparing a compound of formula L^2H-D (I-c-1), wherein L^2 is a geminal bivalent radical comprising C_{3-6} cycloalkylidene, C_{1-12} alkylidene, R^3-C_{1-6} alkylidene, R^4-Y-C_{1-6} alkylidene and $R^5-Z^2-C(=X)-Z^1-C_{1-6}$ alkylidene;

g) alkylating a compound of formula $H-Y-Alk-D$ (I-c-3) with an intermediate of formula $R^{4-a}-W^1$ (XII), wherein R^{4-a} is a Ar² or Het, in a reaction-inert solvent, thus preparing a compound of formula $R^{4-a}-Y-Alk-D$ (I-c-2);

h) alkylating an intermediate of formula $R^{4-a}-Y-H$ (XIII) wherein R^{4-a} is Ar² or Het with a compound of formula $W^1-Alk-D$ (I-c-4), in a reaction-inert solvent, thus preparing a compound of formula (I-c-2);

i) reacting a reagent of formula $R^5-Z^{2-a}-H$ (XIV), wherein Z^{2-a} has the previously defined meaning of Z^2 provided that it is other than a direct bond, with a compound of formula $X=C=N-Alk-D$ (I-c-6), in a reaction-inert solvent, thus preparing a compound of formula $R^5-Z^{2-a}-C(=X)-NH-Alk-D$ (I-c-5);

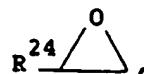
j) reacting an isocyanate or isothiocyanate of formula $R^5-N=C=X$ (XV) with a compound of formula $H-Z^{1-a}-Alk-D$ (I-c-8), wherein Z^{1-a} has the previously defined meaning of Z^1 provided that it is other than a direct bond, in a reaction-inert solvent, thus preparing a compound of formula $R^5-NH-C(=X)-Z^{1-a}-Alk-D$ (I-c-7);

k) reacting a reagent of formula $R^5-C(=X)-OH$ (XVI) with (I-c-8), in a reaction-inert solvent, if desired, after converting the OH group in (XVI) in a reactive leaving group or by reacting (XVI) with (I-c-8) in the presence of a reagent capable of forming esters or amides, thus preparing a compound of formula $R^5-C(=X)-Z^{1-a}-Alk-D$ (I-c-9);

l) reacting an alkenylene of formula L^3-C_{2-6} alkenediyl-H (XVII), wherein L^3 being Ar², Het, Ar²-sulfonyl or a radical of formula $R^5-Z^2-C(=X)-$, with a compound of formula (I-d), in a reaction-inert solvent, thus preparing a compound of formula L^3-C_{2-6} alkanediyl-D (I-c-10);

m) reacting a reagent of formula

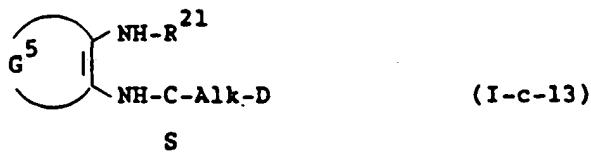
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wherein R^{24} is hydrogen or a radical R^6-O-CH_2- , with a compound of formula (I-d), in a reaction-inert solvent, thus preparing a compound of formula $R^{24}-CH(OH)-CH_2-D$ (I-c-11); or

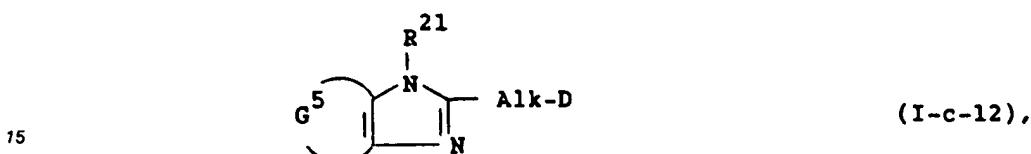
n) cyclodesulfurizing a compound of formula

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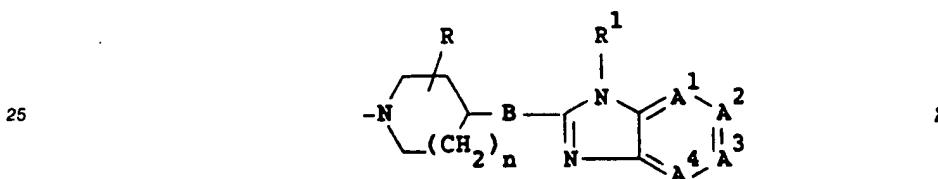
with an alkylhalide, metal oxide or metal salt in a reaction-inert solvent, thus preparing a compound of formula

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wherein G⁵ and R²¹ are as previously defined;
wherein D represents a radical of formula

20



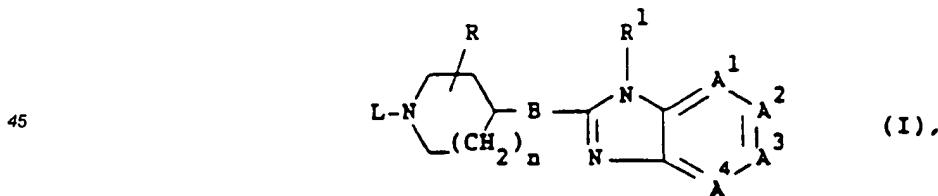
30 wherein -A¹=A²-A³=A⁴-, B, G, R, R¹ and n have the previously described meanings; or optionally converting the compounds of formula (I) into each other following art-known grouptransformation procedures, and, if desired, converting the compounds of formula (I) into a therapeutically active non-toxic acid-addition salt form by treatment with an appropriate acid or, conversely, converting the acid-addition salt into the free base form with alkali; and/or preparing stereochemically isomeric forms thereof.

35

Patentansprüche

1. Chemische Verbindung mit der Formel

40



50 ein pharmazeutisch annehmbares Säureadditionssalz der eine stereochemisch isomere Form hievon, worin:

-A¹=A²-A³=A⁴- einen zweiwertigen Rest mit der Formel

55

- CH=CH-CH=CH- (a-1),
- N=CH-CH=CH- (a-2),
- CH=N-CH=CH- (a-3),
- CH=CH-N=CH- (a-4),
- CH=CH-CH=N- (a-5),

-N = CH-N = CH- (a-6) oder
 -CH = N-CH = N- (a-7)

darstellt, worin ein oder zwei Wasserstoffatome in diesen Resten (a-1) bis (a-7) jeweils unabhängig voneinander durch Halogen, C₁₋₆-Alkyl, C₁₋₆-Alkyloxy, Trifluormethyl oder Hydroxy ersetzt sein können;

R¹ für Wasserstoff, C₁₋₁₀-Alkyl, C₃₋₆-Cycloalkyl, Ar¹ oder durch ein oder zwei Ar¹-Reste substituiertes C₁₋₆-Alkyl steht;

B für NR², CH₂, O, S, SO oder SO₂ steht; wobei der Rest R² Wasserstoff, C₁₋₆-Alkyl, C₃₋₆-Cycloalkyl, C₁₋₆-Alkylcarbonyl, C₁₋₆-Alkyloxycarbonyl oder Ar²-C₁₋₆-Alkyl darstellt;

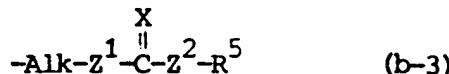
R Wasserstoff der C₁₋₆-Alkyl bedeutet;

n 0 der 2 ist;

L für Wasserstoff, C₁₋₆-Alkylcarbonyl, C₁₋₆-Alkylsulfonyl, C₁₋₆-Alkyloxycarbonyl, Ar²-C₁₋₆-Alkyloxycarbonyl, Ar²-Carbonyl, Ar²-Sulfonyl, C₃₋₆-Cycloalkyl, C₂₋₆-Alkenyl, das gegebenenfalls durch Ar² substituiert ist, C₁₋₁₂-Alkyl, oder einen Rest der Formel

-Alk-R³ (b-1)

-Alk-Y-R⁴ (n-2)



oder

-CH₂-CHOH-CH₂-O- (b-4)

steht, worin

R³ für Ar², Het, Cyano, Isocyanato, Isothiocyanato, Ar²-Sulfonyl oder Halogen steht;

R⁴ Wasserstoff, Ar², Het oder C₁₋₆-Alkyl bedeutet, das gegebenenfalls durch Halogen, Ar² oder Het substituiert ist;

R⁵ Wasserstoff, Ar², Het oder C₁₋₆-Alkyl bedeutet, das gegebenenfalls durch Halogen Ar² oder Het substituiert ist;

R⁶ für Ar²- oder Naphthalinyl steht;

Y für o, s oder NR⁷ steht;

wobei der Rest R⁷ Wasserstoff, C₁₋₆-Alkyl, C₁₋₆-Alkylcarbonyl oder Ar¹-Carbonyl darstellt;

Z¹ und Z² jeweils unabhängig voneinander O, S, NR⁸ oder eine direkte Bindung darstellen;

worin der Rest R⁸ Wasserstoff oder C₁₋₆-Alkyl bedeutet;

X für O, S oder NR⁹ steht;

worin der Rest R⁹ Wasserstoff, C₁₋₆-Alkyl oder Cyano darstellt;

jedes Alk unabhängig voneinander für C₁₋₆-Alkandiyl steht;

Het einen fünf- oder sechsgliedrigen heterocyclischen Ring bezeichnet, der 1, 2, 3 oder 4 Heteroatome enthält, wobei diese Heteroatome aus der aus Sauerstoff, Schwefel und Stickstoff bestehenden Gruppe ausgewählt sind, mit der Maßgabe, daß nicht mehr als zwei Sauerstoff- oder Schwefelatome vorliegen, welcher fünf- oder sechsgliedrige Ring gegebenenfalls mit einer fünf- oder

sechsgliedrigen carbocyclischen oder heterocyclischen Ring kondensiert ist, der ebenfalls 1, 2, 3 oder 4 Heteroatome enthält, wobei die letztgenannten Heteroatome aus der aus Sauerstoff, Schwefel und Stickstoff bestehenden Gruppe ausgewählt sind, mit der Maßgabe, daß nicht mehr als 2 Sauerstoff- oder Schwefelatome vorliegen, und, wenn der Rest Het ein bicyclisches Ringsystem bedeutet, dieses

gewünschtenfalls mit bis zu 6 Substituenten substituiert sein kann, und, wenn der Rest Het ein monocyclisches Ringsystem ist, dieses gewünschtenfalls mit bis zu 3 Substituenten substituiert sein kann, wobei diese Substituenten von Het aus der aus einem zweiseitigen Rest der Formel =X; Halogen; Isocyanato; Isothiocyanato; Nitro; Cyano; Trifluormethyl; eine Rest der Formel -A; eine Rest der Formel -Y-A; oder eine Rest der Formel -Z¹-C(=X)-Z²-A bestehenden Gruppe ausgewählt sind;

worin das erwähnte =X unabhängig die gleiche Bedeutung des zuvor definierten Restes X aufweist und A für Wasserstoff, Ar² oder C₁₋₆-Alkyl steht, des gegebenenfalls durch Ar², C₁₋₆-Alkyloxy, Ar²-O, Hydroxy oder C₁₋₆-Alkyloxycarbonyl substituiert ist; und Y, Z¹ und Z² unabhängig voneinander die gleichen Bedeutungen wie die zuvor definierten Reste Y, Z¹ und Z² aufweisen; mit der Maßgabe, daß

dann, wenn in dem Rest $-Z^1-C(=X)-Z^2-A$ A für Wasserstoff und Z^1 für NR^8 , O oder S stehen, Z^2 eine andere Bedeutung als O oder S aufweist;

Ar¹ ein aus der aus Phenyl, das gegebenenfalls durch 1, 2 oder 3 Substituenten, jeweils unabhängig voneinander ausgewählt aus der aus Halogen, Hydroxy, Nitro, Cyano, Trifluormethyl, C₁₋₆-Alkyl, C₁₋₆-Alkyloxy, C₁₋₆-Alkylthio, Mercapto, Amino, Mono- und Di(C₁₋₆-alkyl)amino, Carboxyl, C₁₋₆-Alkyloxycarbonyl und C₁₋₆-Alkylcarbonyl bestehenden Gruppe, substituiert ist; Thienyl; Halogenthienyl; Furanyl; C₁₋₆-Alkyl-substituiertem Furanyl; Pyridinyl; Pyrimidinyl; Pyrazinyl; Thiazolyl und Imidazolyl, das gegebenenfalls durch C₁₋₆-Alkyl substituiert ist, bestehenden Gruppe ausgewähltes Glied ist; und

Ar² ein aus der aus Phenyl, das gegebenenfalls durch 1, 2 oder 3 Substituenten, die jeweils unabhängig voneinander aus der aus Halogen, Hydroxy, Nitro, Cyano, Trifluormethyl, C₁₋₆-Alkyl, C₁₋₆-Alkyloxy, C₁₋₆-Alkylthio, Mercapto, Amino, Mono- und Di(C₁₋₆-alkyl)amino, Carboxyl, C₁₋₆-Alkyloxycarbonyl und C₁₋₆-Alkylcarbonyl bestehenden Gruppe ausgewählt sind, bestehenden Gruppe ausgewähltes Glied ist.

15 2. Chemische Verbindung nach Anspruch 1, worin n den Wert 2 aufweist.

3. Chemische Verbindung nach Anspruch 1, worin n den Wert 0 hat.

4. Chemische Verbindung nach Anspruch 1, worin

Het für (i) einen gegebenenfalls substituierten fünf- oder sechsgliedrigen heterocyclischen Ring steht, der 1, 2, 3 oder 4 Heteroatome, ausgewählt aus der aus Sauerstoff, Schwefel und Stickstoff bestehenden Gruppe, enthält, mit der Maßgabe, daß nicht mehr als zwei Sauerstoff- oder Schwefelatome vorliegen; oder

Het für (ii) einen gegebenenfalls substituierten fünf- oder sechsgliedrigen heterocyclischen Ring mit einer Gehalt an 1 oder 2 Heteroatomen, ausgewählt aus der aus Sauerstoff, Schwefel und Stickstoff bestehenden Gruppe, steht, der mit einem gegebenenfalls substituierten fünf- oder sechsgliedrigen Ring über zwei Ringkohlenstoffatome oder ein Ringkohlenstoffatom und ein Ringstickstoffatom ortho-kondensiert ist, wobei im restlichen kondensierten Ring nur Kohlenstoffatome vorliegen; oder

Het für (iii) einen gegebenenfalls substituierten fünf- oder sechsgliedrigen heterocyclischen Ring mit einer Gehalt an 1 oder 2 Heteroatomen, ausgewählt aus der aus Sauerstoff, Schwefel und Stickstoff bestehenden Gruppe, steht, der mit einer gegebenenfalls substituierten fünf- oder sechsgliedrigen heterocyclischen Ring über zwei Ringkohlenstoffatome oder ein Ringkohlenstoffatom und ein Ringstickstoffatom ortho-kondensiert ist, wobei im restlichen kondensierten Ring 1 oder 2 Heteroatome, ausgewählt aus der aus Sauerstoff, Schwefel und Stickstoff bestehenden Gruppe, vorliegen; worin der Rest

Het gegebenenfalls durch bis zu 2 Substituenten substituiert sein kann, wenn Het ein monocyclisches Ringsystem ist, und Het gegebenenfalls durch bis zu 5 Substituenten substituiert sein kann, wenn Het ein bicyclisches Ringsystem darstellt, welche Substituenten von Het aus der aus einem zweiwertigen Rest der Formel =X; Halogen; Isocyanato; Isothiocyanato; Nitro; Cyano; Trifluormethyl; einem Rest der Formel -A; einem Rest der Formel -Y-A; oder einem Rest der Formel -Z¹-C(=X)-Z²-A bestehenden Gruppe ausgewählt sind; worin der Rest =X unabhängig die gleiche Bedeutung des zuvor erwähnten Restes X aufweist und A für Wasserstoff, Ar² oder C₁₋₆-Alkyl steht, das gegebenenfalls durch Ar², C₁₋₆-Alkyloxy, Ar²-O, Hydroxy oder C₁₋₆-Alkyloxycarbonyl substituiert ist; und Y, Z¹ und Z² unabhängig voneinander die gleichen Bedeutungen wie die zuvor definierten Reste Y, Z¹ und Z² aufweisen; mit der Maßgabe, daß dann, wenn in dem Rest -Z¹-C(=X)-Z²-A A Wasserstoff bedeutet und Z¹ für NR⁸, O oder S steht, Z² eine andere Bedeutung als O oder S hat.

5. Chemische Verbindung nach Anspruch 4, worin R Wasserstoff ist, R¹ für durch einen Rest Ar¹ substituiertes C₁₋₆-Alkyl steht und B für NH oder CH₂ steht.

50 6. Chemische Verbindung nach Anspruch 5, worin L Wasserstoff, C₁₋₆-Alkyl oder einen Rest der Formel (b-1), (b-2) oder (b-3) bedeutet und B für NH steht.

7. Chemische Verbindung nach Anspruch 6, worin R³, R⁴ und R⁵ jew als Ar² oder Het bedeuten, R⁷ Wasserstoff oder C₁₋₆-Alkyl darstellt, X für O steht und Z¹ und Z² jeweils unabhängig voneinander NH oder eine direkte Bindung bedeuten.

55 8. Pharmazeutische Zusammensetzung, umfassend einen geeigneten pharmazeutischen Träger und als wirksamen Bestandteil eine therapeutisch wirksame Menge einer Verbindung nach einem der Ansprü-

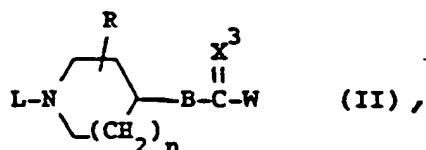
che 1 bis 7.

9. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, dadurch gekennzeichnet, daß eine therapeutisch wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 7 mit geeigneten pharmazeutischen Trägern innig vermischt wird.

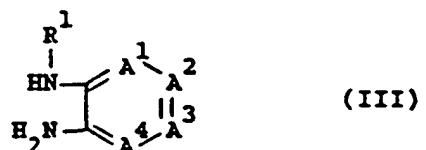
10. Verbindung nach einem der Ansprüche 1 bis 7 zur Verwendung als ein Medikament.

11. Verfahren zur Herstellung einer chemischen Verbindung nach einem der Ansprüche 1 bis 7, gekennzeichnet durch

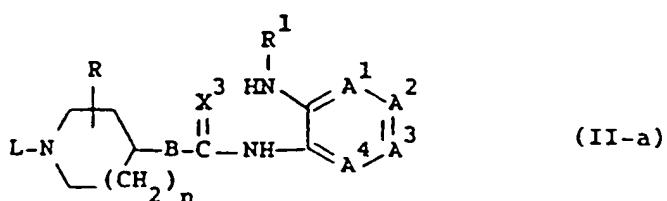
10 a) Umsetzen eines Pyrrolidins oder Hexahydro-1H-azepins der Formel



20 worin X³ für O, S oder NH steht und W eine reaktionsfähige Leaving-Gruppe bedeutet, mit einem aromatischen Diamin der Formel

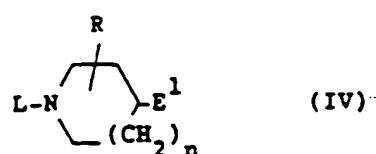


30 in einem reaktionsinerten Medium, welche Umsetzung in einigen Fällen über ein Zwischenprodukt der Formel



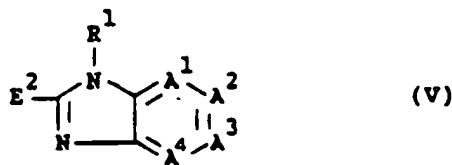
45 verläuft, das in situ oder gewünschtenfalls nach einem Isolieren und weiteren Reinigen zu den gewünschten Verbindungen der Formel (I) cyclisiert werden kann;

b) Umsetzen eines Pyrrolidins oder Hexahydro-1H-azepins der Formel



55 mit einem Zwischenprodukt der Formel

5



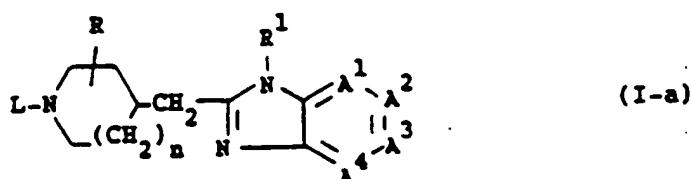
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in einem reaktionsinerten Lösungsmittel, gewünschtenfalls in Anwesenheit eines Reduktionsmittels, worin:

15

- i) E¹ einen Rest der Formel -B-M bedeutet, worin M Wasserstoff oder ein Alkalimetall oder Erdalkalimetall darstellt und E² eine Rest der Formel -W darstellt; oder
- ii) E¹ einen Rest der Formel -W¹ bezeichnet und E² einen Rest der Formel M-B- darstellt; oder
- iii) E¹ einen Rest der Formel -CH₂-W¹ bezeichnet und E² einen Rest der Formel -M darstellt, wodurch eine Verbindung der Formel

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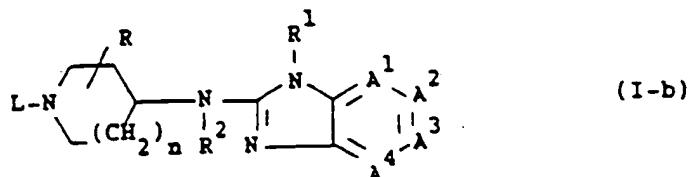


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- bereitet wird; oder
- iv) E¹ einen Rest der Formel -M bezeichnet und E² einen Rest der Formel -CH₂-W¹ darstellt, wodurch eine Verbindung der Formel (I-a) erhalten wird; oder
- v) E¹ einen Rest der Formel =O bezeichnet und E² einen Rest der Formel R²-NH- darstellt, wodurch eine Verbindung der Formel

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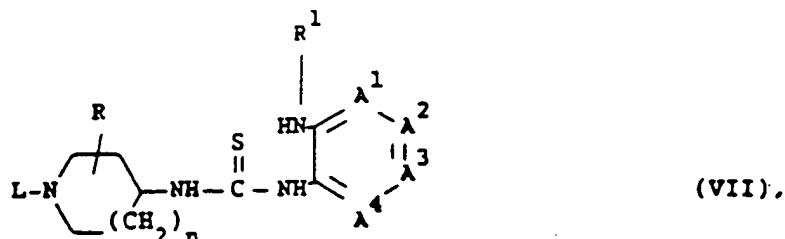


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- hergestellt wird; oder
- c) Cyclodesulfurieren eines Zwischenprodukts der Formel

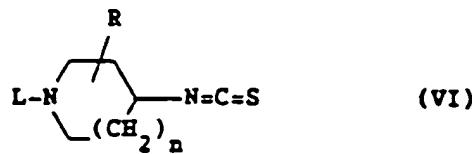
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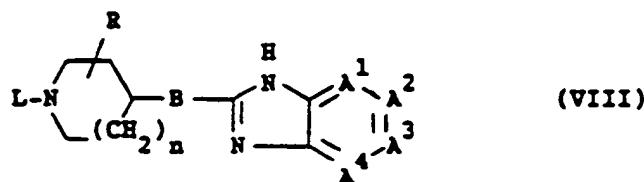


das *in situ* durch Kondensieren eines Isothiocyanats der Formel

55



mit einem Diamin der Formel (III) hergestellt werden kann,
mit einem Alkylhalogenid, Metallocid oder Metallsalz in einem reaktionsinerten Lösungsmittel;
d) N-Alkylieren eines Zwischenprodukts der Formel



20 mit einer Reagens der Formel



25 worin W¹ eine reaktionsfähige Leaving-Gruppe bezeichnet, in einem reaktionsinerten Medium; oder
e) N-Alkylieren einer Verbindung der Formel H-D (I-d) mit einem Reagens der Formel L¹-W¹ (X) in
einem reaktionsinerten Lösungsmittel, unter Ausbildung einer Verbindung der Formel L¹-D (I-c),
worin L¹ die zuvor definierte Bedeutung von L aufweist, mit der Maßgabe, daß L¹ von Wasserstoff
verschieden ist;

30 f) reduktives N-Alkylieren einer Verbindung der Formel H-D (I-d) mit einem Keton oder Aldehyd der
Formel L²=O (XI), worin das genannte L²=O ein Intermediärprodukt der Formel L²H₂ ist, worin zwei
geminale Wasserstoffatome durch =O ersetzt sind, in einem reaktionsinerten Medium unter Ausbil-
dung einer Verbindung der Formel L²H-D (I-c-1), worin L² einen geminalen zweiwertigen Rest,
umfassend C₃-6-Cycloalkylen, C₁-12-Alkylen, R³-C₁-6-Alkylen, R⁴-Y-C₁-6-Alkylen und R⁵-
Z²-C(=X)-Z¹-C₁-6-Alkylen, darstellt;

35 g) Alkylieren einer Verbindung der Formel H-Y-Alk-D (I-c-3) mit einem Zwischenprodukt der Formel
R^{4-a}-W¹ (XIII), worin R^{4-a} für Ar² oder Het steht, in eine reaktionsinerten Lösungsmittel unter
Ausbildung einer Verbindung der Formel R^{4-a}-Y-Alk-D (I-c-2);

40 h) Alkylieren eines Zwischenprodukts der Formel R^{4-a}-Y-H (XIII), worin R^{4-a} für Ar² oder Het steht, mit
einer Verbindung der Formel W¹-Alk-D (I-c-4) in einem reaktionsinerten Lösungsmittel unter Ausbil-
dung einer Verbindung der Formel (I-c-2);

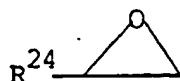
45 i) Umsetzen eines Reagens der Formel R⁵-Z^{2-a}-H (XIV), worin Z^{2-a} die zuvor für Z² angegebene
Bedeutung aufweist, mit der Maßgabe, daß es sich nicht um eine direkte Bindung handelt, mit einer
Verbindung der Formel X=C=N-Alk-D (I-c-6) in einem reaktionsinerten Lösungsmittel unter Ausbil-
dung einer Verbindung der Formel R⁵-Z^{2-a}-C(=X)-NH-Alk-D (I-c-5);

j) Umsetzen eines Isocyanats oder Isothiocyanats der Formel R⁵-N=C=X (XV) mit einer Verbindung
der Formel H-Z^{1-a}-Alk-D (I-c-8), worin Z^{1-a} die zuvor für Z¹ angegebene Bedeutung mit der Maßgabe
hat, daß eine andere Bedeutung als eine direkte Bindung vorliegt, in einem reaktionsinerten
Lösungsmittel unter Ausbildung einer Verbindung der Formel R⁵-NH-C(=X)-Z^{1-a}-Alk-D (I-c-7);

50 k) Umsetzen eines Reagens der Formel R⁵-C(=X)-OH (XVI) mit (I-c-8) in einem reaktionsinerten
Lösungsmittel, gewünschtenfalls nach Umwandeln der OH-Gruppe in (XVI) in eine reaktionsfähige
Leaving-Gruppe oder durch Umsetzen von (XVI) mit (I-c-8) in Anwesenheit eines zur Bildung von
Estern oder Amiden befähigten R agens unter Ausbildung einer Verbindung der Formel R⁵-C(=X)-
Z^{1-a}-Alk-D (I-c-9);

55 l) Umsetzen eines Alkenylens der Formel L³-C₂-6-Alkendiyl-H (XVII), worin L³ für Ar², Het, Ar²-
Sulfonyl oder einen Rest der Formel R⁵-Z²-C(=X)- steht, mit einer Verbindung der Formel (I-d) in
einem reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel L³-C₂-6-
Alkandiyl-D (I-c-10);

m) Umsetzen eines Reagens der Formel

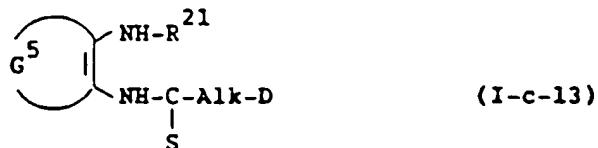


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worin R²⁴ für Wasserstoff oder einen Rest R⁶-O-CH₂- steht, mit einer Verbindung der Formel (I-d) in einem reaktionsinternen Lösungsmittel unter Ausbildung einer Verbindung der Formel R²⁴-CH(OH)-CH₂-D (I-c-11); oder

10

n) Cyclodesulfurieren einer Verbindung der Formel



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mit einem Alkylhalogenid, Metalloxid oder Metallsalz in einem reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel

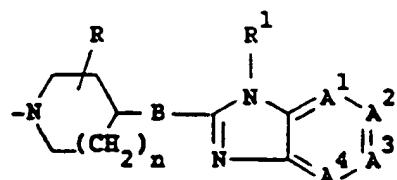


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worin G^5 und R^{21} wie zuvor definiert sind;

worin D einen Rest der Formel



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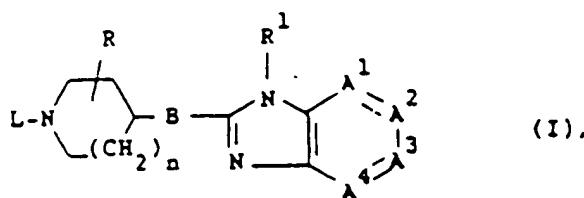
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bezeichnet:

worin $-A^1 = A^2 - A^3 = A^4$ -, B, G, R, R¹ und n die zuvor angegebenen Bedeutungen aufweisen; oder gewünschtenfalls Umwandeln der Verbindungen der Formel (I) ineinander nach Bekannten Gruppentransformationsverfahren, und gewünschtenfalls Umwandeln der Verbindungen der Formel (I) in eine therapeutisch wirksame nicht-toxische Säureadditionssalzform durch Behandeln mit einer entsprechenden Säure oder, umgekehrt, Umwandeln des Säureadditionssalzes in die freie Basenform mit Alkali; und/oder Herstellen stereochemisch isomerer Formen hievon.

50 Revendications

1. Composé chimique de formule



10 un de ses sels d'addition d'acides pharmaceutiquement acceptables ou formes stéréochimiquement
isomériques; où
-A¹ = A²-A³ = A⁴- est un radical bivalent de formule

15 -CH=CH-CH=CH- (a-1),
-N=CH-CH=CH- (a-2),
-CH=N-CH=CH- (a-3),
-CH=CH-N=CH- (a-4),
-CH=CH-CH=N- (a-5),
-N=CH-H=CH- (a-6), ou
20 -CH=N-CH=N- (a-7),

dans laquelle un ou deux atomes d'hydrogène dans lesdits radicaux (a-1) - (a-7) peut(peuvent) chacun
indépendamment l'un de l'autre être remplacés par un halo, alcoyle en C₁₋₆, alcoyloxy en C₁₋₆,
trifluorométhyle ou hydroxy ;

25 R¹ est un hydrogène, alcoyle en C₁₋₁₀, cycloalcoyle en C₃₋₆, Ar¹ ou alcoyle en C₁₋₆ substitué par
un ou deux radicaux Ar¹ ;

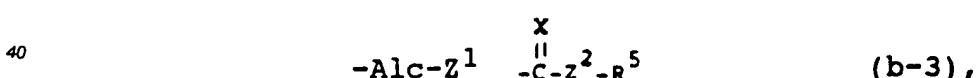
B représente NR², CH₂, O, S, SO ou SO₂ ; ledit R² étant un hydrogène, alcoyle en C₁₋₆,
cycloalcoyle en C₃₋₆, alcoyle en C₁₋₆-carbonyle, alcoyloxy en C₁₋₆-carbonyle et Ar²-alcoyle en C₁₋₆ ;

R est un hydrogène ou un alcoyle en C₁₋₆ ;

30 n vaut 0 ou 2 ;

L est un hydrogène, alcoyle en C₁₋₆-carbonyle, alcoyle en C₁₋₆-sulfonyle, alcoyloxy en C₁₋₆-
carbonyle, Ar²-alcoyloxy en C₁₋₆-carbonyle, Ar²-carbonyle, Ar²-sulfonyle, cycloalcoyle en C₃₋₆, alcény-
le en C₂₋₆ éventuellement substitué par Ar², alcoyle en C₁₋₁₂, un radical de formule

35 -Alc-R³ (b-1)
-Alc-Y-R⁴ (b-2)



ou

-CH₂-CHOH-CH₂-O-R⁶ (b-4) ;

45 dans laquelle

R³ représente Ar², Het, cyano, isocyanato, isothiocyanato, Ar²-sulfonyle ou halo ;

R⁴ est un hydrogène, Ar², Het, ou alcoyle en C₁₋₆ éventuellement substitué par un halo, Ar² ou Het

;

50 R⁵ est un hydrogène, Ar², Het ou alcoyle en C₁₋₆ éventuellement substitué par un halo, Ar² ou Het

;

R⁶ est un Ar² ou un naphtalényle ;

Y représente O, S, NR⁷ ;

ledit R⁷ étant un hydrogène, alcoyle en C₁₋₆, alcoyle en C₁₋₆-carbonyle ou Ar¹-carbonyle ;

55 Z¹ et Z² représentent chacun indépendamment O, S, NR⁸ ou une liaison directe;

ledit R⁸ étant un hydrogène ou un alcoyle en C₁₋₆ ;

X représente O, S ou NR⁹ ;

ledit R⁹ est un hydrogène, alcoyle en C₁₋₆ ou cyano,

chaque Alc représente indépendamment un alcane en C₁₋₆-diyle ;

Het est un noyau hétérocyclique à cinq ou six chaînons contenant 1, 2, 3 ou 4 hétéroatomes, lesdits hétéroatomes étant choisis dans le groupe constitué par l'oxygène, le soufre et l'azote, à condition que pas plus de deux oxygènes ou soufres soient présents, ledit noyau à cinq ou six chaînons étant facultativement condensé avec un noyau carbocyclique ou hétérocyclique à cinq ou six chaînons contenant également 1, 2, 3, ou 4 hétéroatomes, ces derniers hétéroatomes étant choisis dans le groupe constitué par l'oxygène, le soufre et l'azote, à condition que pas plus de deux atomes d'oxygène ou de soufre soient présents, et lorsque ledit Het est un système bicyclique, il peut être facultativement substitué par jusqu'à six substituants, et lorsque ledit Het est un système cyclique monocyclique, il peut facultativement être substitué par jusqu'à trois substituants, lesdits substituants de Het étant choisis dans le groupe constitué par un radical bivalent de formule =X ; halo ; isocyanato ; isothiocyanato ; nitro ; cyano ; trifluorométhyle ; un radical de formule -A ; un radical de formule -Y-A ; ou un radical de formule -Z¹-C(=X)-Z²-A ; où ledit =X a indépendamment la même signification que celle de X définie ci-dessus et A est hydrogène, Ar² ou un alcoyle en C₁₋₆ éventuellement substitué par Ar², alcoyoxy en C₁₋₆, Ar²-O, hydroxy ou alcanoxy en C₁₋₆-carbonyle ; et Y, Z¹ et Z² ont indépendamment la même signification que celle de Y définie ci-dessus, Z¹ et Z² ; à condition que lorsque dans le radical -Z¹-C(=X)-Z²-A, A est un hydrogène et Z¹ est NR⁸, O ou S, alors Z² est différent de O ou S ;

Ar¹ est un membre choisi dans le groupe constitué par phényle, éventuellement substitué par 1, 2 ou 3 substituants, chacun choisi dans le groupe constitué par halo, hydroxy, nitro, cyano, trifluorométhyle, alcoyle en C₁₋₆, alcoyoxy en C₁₋₆, alcoylthio en C₁₋₆, mercapto, amino, mono- et di(alcoyle en C₁₋₆)amino, carboxyle, alcoyoxy en C₁₋₆-carbonyle et alcoyle en C₁₋₆-carbonyle ; thiényle ; halothiényle ; furanyle ; furanyle substitué par un alcoyle en C₁₋₆ ; pyridinyle ; pyrimidinyle ; pyrazinyle ; thiazolyle et imidazolyle, éventuellement substitué par un alcoyle en C₁₋₆ ; et

Ar² est un membre choisi dans le groupe constitué par phényle éventuellement substitué par 1, 2 ou 3 substituants chacun choisi indépendamment dans le groupe constitué par halo, hydroxy, nitro, cyano, trifluorométhyle, alcoyle en C₁₋₆, alcoyoxy en C₁₋₆, alcoylthio en C₁₋₆, mercapto, amino, mono- et di(alcoyle en C₁₋₆)amino, carboxyle, alcoyoxy en C₁₋₆-carbonyle et alcoyle en C₁₋₆-carbonyle.

30 2. Composé chimique selon la revendication 1, dans lequel n = 2.

3. Composé chimique selon la revendication 1, dans lequel n = 0.

4. Composé chimique selon la revendication 1, dans lequel Het représente (i) un noyau hétérocyclique à 5 ou 6 chaînons substitué contenant 1, 2, 3 ou 4 hétéroatomes choisis dans le groupe constitué par l'oxygène, le soufre et l'azote, à condition qu'il n'y ait pas plus de deux atomes d'oxygène ou de soufre présents ; ou Het est (ii) un noyau hétérocyclique à 5 ou 6 chaînons éventuellement substitué contenant un ou deux hétéroatomes choisis dans le groupe constitué par l'oxygène, le soufre et l'azote, étant condensé en ortho avec un noyau à 5 ou 6 chaînons éventuellement substitué par deux atomes de carbone du cycle ou un atome de carbone du cycle et un atome d'azote du cycle, ne contenant dans le reste du noyau condensé que des atomes de carbone ; ou

Het est (iii) un noyau hétérocyclique à 5 ou 6 chaînons éventuellement substitué contenant un ou deux hétéroatomes choisis dans le groupe constitué par l'oxygène, le soufre et l'azote, étant condensé en ortho avec un noyau hétérocyclique à 5 ou 6 chaînons éventuellement substitué par deux atomes de carbone du cycle ou un atome de carbone du cycle et un atome d'azote du cycle, contenant dans le reste du noyau condensé un ou deux hétéroatomes choisis dans le groupe constitué par l'oxygène, le soufre et l'azote ; où Het peut être éventuellement substitué par jusqu'à deux substituants lorsque Het est un système cyclique monocyclique et où Het peut éventuellement être substitué par jusqu'à cinq substituants lorsque Het est cyclique bicyclique, lesdits substituants étant choisis dans le groupe constitué par un radical bivalent de formule =X, halo, isocyanato ; isothiocyanato ; nitro, cyano ; trifluorométhyle ; un radical de formule -A ; un radical de formule -Y-A ; ou un radical de formule -Z¹-C(=X)-Z²-A ; où ledit =X a indépendamment la même signification que celle de X définie ci-dessus et A est un hydrogène, Ar² ou un alcoyle en C₁₋₆ éventuellement substitué par Ar², alcoyoxy en C₁₋₆, Ar²-O, hydroxy ou alcoyoxy en C₁₋₆-carbonyle ; et Y, Z¹ et Z² ont indépendamment la même signification que celle de Y, Z¹ et Z² définie ci-dessus ; à condition que lorsque dans le radical -Z¹-C(=X)-Z²-A, A est un hydrogène et Z¹ est NR⁸, O ou S, alors Z² est différent de O ou S.

5. Composé chimique selon la revendication 4, dans lequel R est hydrogène, R¹ est un alcoyle en C₁₋₆

substitué par un Ar¹ et B représente NH ou CH₂.

6. Composé chimique selon la revendication 5, dans lequel L est un hydrogène, alcoyle en C₁₋₆ ou un radical (b-1), (b-2) ou (b-3) et B représente NH.

5 7. Composé chimique selon la revendication 6, dans lequel R³, R⁴ et R⁵ représentent chacun Ar² ou Het, R⁷ est un hydrogène ou un alcoyle en C₁₋₆, X représente O, et Z¹ et Z² représentent chacun indépendamment NH ou une liaison directe.

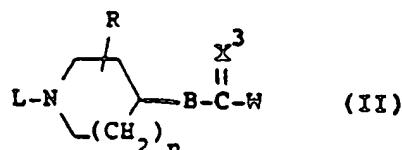
10 8. Composition pharmaceutique comprenant un support pharmaceutique approprié et comme ingrédient actif une quantité thérapeutiquement efficace d'un composé selon l'une des revendications 1 à 7.

15 9. Procédé de préparation d'une composition pharmaceutique caractérisé en ce qu'on mélange intimement une quantité thérapeutiquement efficace d'un composé tel que défini dans l'une quelconque des revendications 1 à 7 avec des supports pharmaceutiques appropriés.

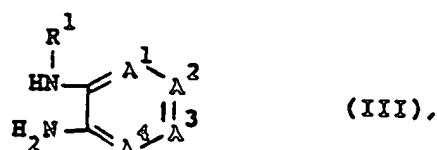
10. Composé selon l'une quelconque des revendications 1 à 7, aux fins d'application comme médicament.

20 11. Procédé de préparation d'un composé chimique selon l'une quelconque des revendications 1 à 7, caractérisé en ce que

20 a) on fait réagir une pyrrolidine ou hexahydro-1H-azépine de formule

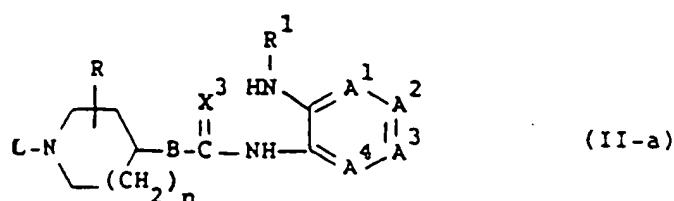


30 dans laquelle X³ représente O, S ou NH et W est un groupe sortant réactif, avec une diamine aromatique de formule



40 dans milieu inerte vis-à-vis de la réaction, ladite réaction se déroulant dans certains cas via un intermédiaire de formule

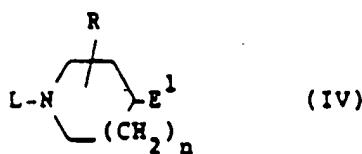
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55 qui peut in situ ou si on le désire après qu'on l'ait isolé et purifié plus avant, être cyclisé pour donner les composés désirés de formule (I) ;

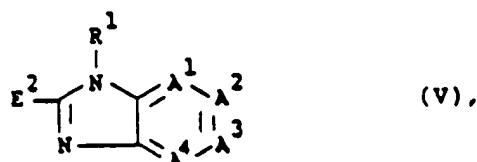
b) On fait réagir une pyrrolidine ou hexahydro-1H-azépine de formule

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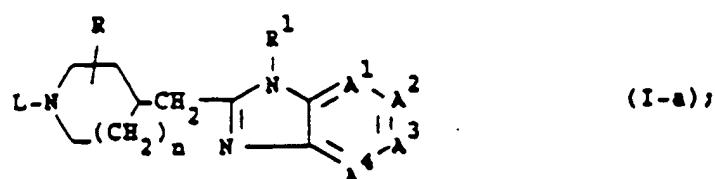


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dans un solvant inerte vis-à-vis de la réaction, si on le désire en présence d'un réducteur, où :

- i) E^1 est un radical de formule $-B-M$ où M est un hydrogène ou un métal alcalin ou alcalino-terreux et E^2 est un radical de formule $-W$;
ou
- ii) E^1 est un radical de formule $-W^1$ et E^2 est un radical de formule $M-B-$; ou
- iii) E^1 est un radical de formule $-CH_2-W^1$ et E^2 est un radical de formule $-M$, préparant ainsi un composé de formule

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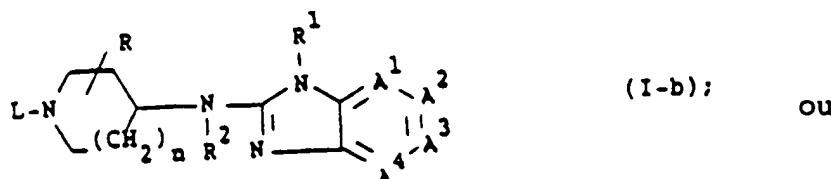
ou

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- iv) E^1 est un radical de formule $-M$ et E^2 est un radical de formule $-CH^2-W^1$, préparant ainsi un composé de formule (I-a) ; ou
- v) E^1 est un radical de formule $=O$ et E^2 est un radical de formule R^2-NH- , préparant ainsi un composé de formule

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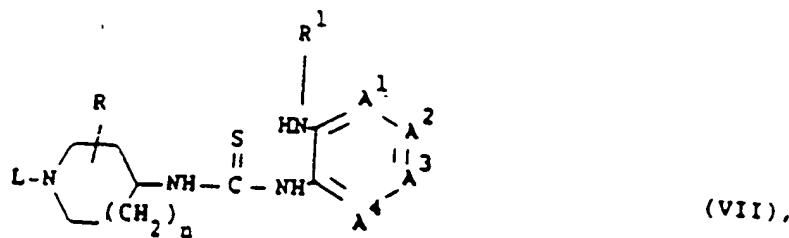


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- c) On cyclodésulfurise un intermédiaire de formule

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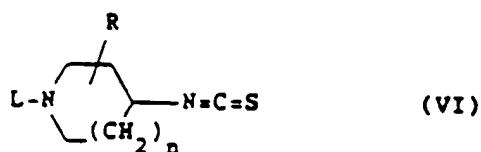
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qui peut être préparé in situ en condensant un isothiocyanate de formule

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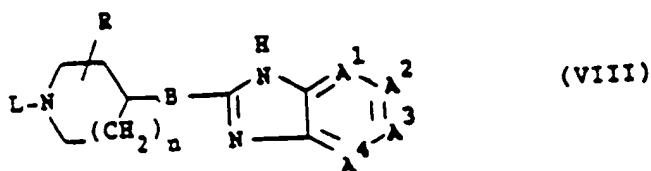
avec une diamine de formule (III),

avec un halogénure d'alcoyle, un oxyde métallique ou un sel métallique dans un solvant inerte vis-à-vis de la réaction ;

d) On N-alcoyle un intermédiaire de formule

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avec un réactif de formule

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$W^1 \cdot R^1$ (IX)

où W^1 est un groupe sortant réactif, dans un milieu inerte vis-à-vis de la réaction ; ou

e) On N-alcoyle un composé de formule H-D (I-d) avec un réactif de formule $L^1 \cdot W^1$ (X) dans un solvant inerte vis-à-vis de la réaction, préparant ainsi un composé de formule $L^1 \cdot D$ (I-c), où L^1 a la signification de L définie ci-dessus, à condition qu'il soit différent d'un hydrogène ;

f) On N-alcoyle de façon réductrice un composé de formule H-D (I-d) avec une cétone ou un aldéhyde de formule $L^2 = O$ (XI), ledit $L^2 = O$ étant un intermédiaire de formule $L^2 H$ où deux atomes d'hydrogène géminés sont remplacés par =O dans un milieu inerte vis-à-vis de la réaction, préparant ainsi un composé de formule $L^2 H \cdot D$ (I-c-1), où L^2 est un radical bivalent géminé comprenant un cycloalcoyliidène en C₃₋₆, alcoyliidène en C₁₋₁₂, R³-alcoyliidène en C₁₋₆, R⁴-Y-alcoyliidène en C₁₋₆ et R⁵-Z²-C(=X)-Z¹-alcoyliidène en C₁₋₆ ;

g) On alcoyle un composé de formule H-Y-Alc-D (I-c-3) avec un intermédiaire de formule $R^{4-a} \cdot W^1$ (XII), où R^{4-a} représente Ar² ou Het, dans un solvant inerte vis-à-vis de la réaction, préparant ainsi un composé de formule $R^{4-a} \cdot Y \cdot Alc \cdot D$ (I-c-2) ;

h) On alcoyle un intermédiaire de formule $R^{4-a} \cdot Y \cdot H$ (XIII) où R^{4-a} représente Ar² ou Het avec un composé de formule $W^1 \cdot Alc \cdot D$ (I-c-4), dans un solvant inerte vis-à-vis de la réaction, préparant ainsi un composé de formule (I-c-2) ;

i) On fait réagir un réactif de formule $R^5 \cdot Z^{2-a} \cdot H$ (XIV), où Z^{2-a} a la signification préalablement définie de Z², à condition qu'il soit différent d'une liaison directe, avec un composé de formule X=C=N-Alc-D (I-c-6) dans un solvant inerte vis-à-vis de la réaction, préparant ainsi un composé de formule $R^5 \cdot Z^{2-a} \cdot C(=X) \cdot NH \cdot Alc \cdot D$ (I-c-5) ;

j) On fait réagir un isocyanate ou isothiocyanate de formule $R^5 \cdot N=C=X$ (XV) avec un composé de

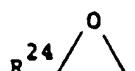
formule $H-Z^{1-a}-Alc-D$ (I-c-8), où Z^{1-a} a la signification préalablement définie de Z^1 à condition qu'il soit différent d'une liaison directe, dans un solvant inerte vis-à-vis de la réaction, préparant ainsi un composé de formule $R^5-NH-C(=X)-Z^{1-a}-Alc-D$ (I-c-7) ;

5 k) On fait réagir un réactif de formule $R^5-C(=X)-OH$ (XVI) avec (I-c-8) dans un solvant inerte vis-à-vis de la réaction, si on le désire, après avoir transformé le groupe OH dans (XVI) en un groupe sortant réactif ou en faisant réagir (XVI) avec (I-c-8) en présence d'un réactif capable de former des esters ou des amides, préparant ainsi un composé de formule $R^5-C(=X)-Z^{1-a}-Alc-D$ (I-c-9) ;

10 l) On fait réagir un alcénylène de formule L^3 -alcène en C_{2-6} -diyle-H-(XVII) où L^3 représente Ar^2 , Het, Ar^2 -sulfonyle ou un radical de formule $R^5-Z^2-C(=X)-$, avec un composé de formule (I-d), dans un solvant inerte vis-à-vis de la réaction, préparant ainsi un composé de formule L^3 -alcane en C_{2-6} -diyle-D (I-c-10) ;

m) On fait réagir un réactif de formule

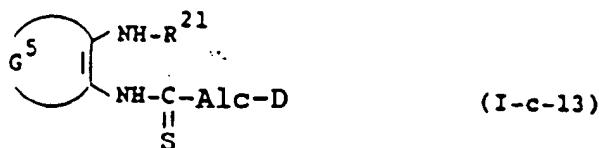
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où R^{24} est un hydrogène ou un radical $R^6-O-CN_2^-$, avec un composé de formule (I-d), dans un solvant inerte vis-à-vis de la réaction, préparant ainsi un composé de formule $R^{24}-CH(OH)-CH_2-D$ (I-c-11) ; ou

n) On cyclodésulfure un composé de formule

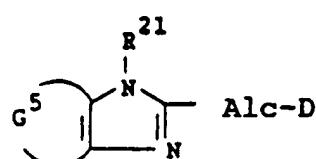
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avec un halogénure d'alcoyle, un oxyde métallique ou un sel métallique, dans un solvant inerte vis-à-vis de la réaction, préparant ainsi un composé de formule

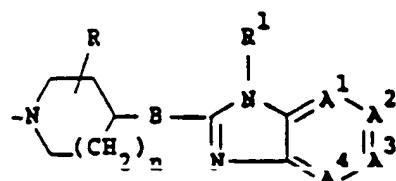
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où G^5 et R^{21} sont tels que définis ci-dessus ;
où D représente un radical de formule

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55 dans laquelle $-A^1 = A^2 - A^3 = A^4 -$, B, G, R, R¹ et n ont les significations définies ci-dessus ; ou, si on le désire, on transforme les composés de formule (I) les uns dans les autres en suivant des procédés connus des spécialistes de transformation des groupes et, si on le désire, on transforme les composés de formule (I) en une forme sel d'addition d'acides non toxique thérapeutiquement active par traitement avec un acide approprié ou, inversement, on transforme le sel d'addition d'acides en la forme base

libre avec une base ; et/ou on prépare ses formes stéréochimiquement isomériques.

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